United States
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Office of Research
and Development
Washington, DC 20460

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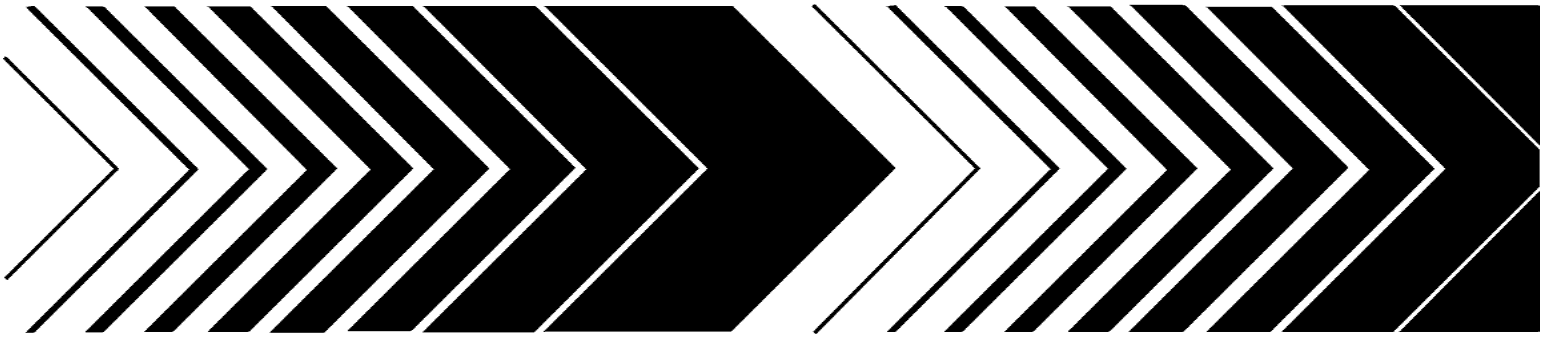
Internal Review Draft

EPA

Human Health Research Strategy

Notice

This document is a preliminary draft. It has not been formally released by EPA and should not at this stage be construed to represent Agency policy. It is being circulated for comment on its technical accuracy and policy implications.



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Disclaimer

This document is a work in progress and is being circulated for review purposes only. It does not constitute an Agency position or policy concerning human health risk assessment research. Any mention of trade names does not constitute Agency endorsement.

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ABBREVIATIONS AND ACRONYMS

ATSDR	Agency for Toxic Substance and Disease Registry
BBDR	Biologically Based Dose Response Modeling
CDC	Centers for Disease Control and Prevention
DBPs	Disinfection By-Products
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FQPA	Food Quality Protection Act
GAO	U.S. General Accounting Office
GPRA	Government Performance and Results Act
NAS	National Academy of Science
NCEA	National Center for Environmental Assessment (EPA/ORD)
NCER	National Center for Environmental Research (EPA/ORD)
NERL	National Exposure Research Laboratory (EPA/ORD)
NHANES	National Health and Nutrition Examination Survey
NHEERL	National Health and Environmental Effects Research Laboratory (EPA/ORD)
NHEP	National Human Exposure Program
NHEXAS	National Human Exposure Assessment Survey
NIOSH	National Institute for Occupational Safety and Health
NRC	National Research Council (NAS)
NRMRL	National Risk Management Research Laboratory (EPA/ORD)
ORD	Office of Research and Development (EPA)
PAH	Polycyclic Aromatic Hydrocarbon
PBPK	Physiologically Based Pharmacokinetic Modeling
PCB	Polychlorinated Biphenyl
PM	Particulate Matter
RfC	Reference Concentration
RfD	Reference Dose
SAB	EPA's Science Advisory Board
SAR	Structure-Activity Relationship
SHEDS	Stochastic Human Exposure and Dose Simulation Model
STAR	EPA/ORD Science to Achieve Results Extramural Grants Program
TEF	Toxic Equivalent Factor
UF	Uncertainty Factor
VOC	Volatile Organic Compound
WHO	World Health Organization

GLOSSARY

Aggregate Exposure: The combined exposure of an individual or defined population to a specific agent or stressor via relevant routes, pathways, and sources (working definition developed by EPA Science Policy Council).

Aggregate Risk: The risk resulting from aggregate exposure to a single agent or stressor (working definition developed by EPA Science Policy Council).

Biological Markers or Biomarkers: Indicator signaling events in biological systems or samples. There are three classes of biomarkers: exposure, effect, and susceptibility. A marker of exposure is an exogenous substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism. A marker of effect is a measurable biochemical, physiological, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease. A marker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic.

Biologically-Based Dose Response (BBDR) Model: A model that describes biological processes at the cellular and molecular level linking the target organ dose to the adverse effect.

Childhood: Nominally, the period from birth through the onset of puberty. However, the Human Health Research Strategy addresses adverse effects on the developing organism that may result from exposure to environmental agents, starting with preconception exposures to parents and continuing through gestation and postnatally up to the time of maturation of all organ systems.

Cumulative Risk: The combined risks from aggregate exposures to multiple agents or stressors (working definition developed by EPA Science Policy Council).

Dose: The amount of a substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism. The potential dose is the amount ingested, inhaled, or applied to the skin. The *applied dose* is the amount of a substance presented to an absorption barrier and available for absorption (although not necessarily having crossed the outer boundary of the organism). The *absorbed dose* is the amount crossing a specific absorption barrier (e.g., the exchange boundaries of the skin, lung, and digestive tract) through uptake processes. *Internal dose* is a more general term denoting the amount absorbed without respect to specific absorption barriers or exchange boundaries. The amount of the pollutant available for interaction by any particular organ or cell is termed the *biologically effective dose* for that organ or cell.

Effectiveness: The improvement in health outcome that a prevention strategy can produce in typical community-based settings.

Efficacy: The improvement in health outcome that a prevention strategy can produce in expert hands under ideal circumstances

Exposure: Contact of a pollutant, physical, or biological agent with the outer boundary of an organism; exposure is quantified as the concentration of the agent in the medium over time.

Margin of Exposure: The ratio of the critical NOAEL to the expected human exposure level.

Mechanism of Action: The complete sequence of biological events that must occur to produce a toxic effect.

Mode of Action (MOA): A less-detailed description of the mechanism of action in which some, but not all, of the sequence of biological events leading to a toxic effect is known.

Nonthreshold Effect: An effect for which it is assumed that there is no dose, no matter how low, for which the probability of an individual's responding is zero.

No-Observed-Adverse-Effect Level (NOAEL): The highest exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control.

Outcome Measure: The final health consequence (e.g., cases prevented, quality-adjusted life years) of an intervention.

Pharmacodynamics: The determination and quantification of the sequence of events at the cellular and molecular levels leading to a toxic response to an environmental agent (also called toxicodynamics).

Pharmacokinetics: The determination and quantification of the time course of absorption, distribution, biotransformation, and excretion of pollutants (also called toxicokinetics).

Physiologically-Based Pharmacokinetic (PBPK) Model: A model that estimates the dose to a target tissue or organ by taking into account the rate of absorption into the body, distribution between target organs and tissues, metabolism, and excretion.

Program Office: An EPA organizational unit that administers a major EPA program (i.e., Air and Radiation; Water; Prevention, Pesticides, and Toxic Substances; and Solid Waste and Emergency Response).

Reference Concentration: An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subpopulations) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime.

Reference Dose: An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subpopulations) that is likely to be without an appreciable risk of deleterious noncancer effects during a lifetime.

Susceptibility: Increased likelihood of an adverse effect related to intrinsic (i.e., life stage, genetic predisposition) or extrinsic determinants (i.e., preexisting disease) unique to the organism.

Threshold Effect: An effect for which there is some dose below which the probability of an individual's responding is zero.

Uncertainty Factor (UF): One of several factors used in calculating an exposure level that will not cause toxicity from experimental data. For example, UF's are used to account for the variation in susceptibility among humans, the uncertainty in extrapolating from experimental animal data to humans, and the uncertainty in extrapolating data from studies in which agents are given for less than a lifetime.

Vulnerability: Synonymous with susceptibility

EXECUTIVE SUMMARY

The mission of the U.S. Environmental Protection Agency (EPA) is to protect public health and safeguard the natural environment. Risk assessment is an integral part of this mission in that it identifies and characterizes environmentally related human health problems. The *Human Health Research Strategy* document presents a conceptual framework for future human health research by EPA's Office of Research and Development (ORD). This research strategy outlines ORD's core research effort to provide broader, more fundamental information that will improve understanding of problem-driven health risk issues encountered by the EPA's Program and Regional Offices. The scope of this research document is strategic in that it discusses broad themes and general approaches. Implementation of an integrated research program on human health is described in greater detail in ORD's Multiyear Plan on Human Health Research. The Multiyear Plan identifies specific performance goals and the measures needed to achieve those goals over a 5 to10 year period. Each Laboratory and Center in ORD is also developing an approach linking research at the project level to the goals and measures in the Multiyear Plan and the general themes outlined in this research strategy document.

Based on the needs of the EPA's Program and Regional offices, recommendations made by external advisory groups, and goals established by EPA in response to the Government Performance and Result Act (GPRA) under Sound Science (Goal 8), ORD has identified two strategic research directions that will be pursued over the next 5 to 10 years (see text box).

Strategic Research Directions

- ❑ Research to Improve the Scientific Foundation of Human Health Risk Assessment, including:
  - Harmonizing Cancer and Noncancer Risk Assessments
  - Assessing Aggregate and Cumulative Risk
  - Determining Risk to Susceptible Human Subpopulations
- ❑ Research to Enable Evaluation of Public Health Outcomes from Environmental Risk Management Decisions.

Research in these strategic areas will improve the scientific foundation for EPA's risk assessments and lead to principles that can be used to evaluate the effectiveness of risk management actions aimed at improving environmental public health. Chapter 1 of the *Human Health Research Strategy* document provides background information regarding the regulatory and scientific basis for a core research program on human health risk assessment. Chapter 1 also develops the need for a multidisciplinary, integrated research program and how ORD will formulate problems and approaches to study complex questions related to human health. Chapter 2 describes the scientific uncertainties, objectives and approaches that ORD will use to harmonize risk assessments, assess aggregate and cumulative risk, and determine risk to susceptible subpopulations. Chapter 3 describes ORD's public health outcomes research program, which will work toward providing more scientifically defensible assessments of *actual* reduction in risk.

ORD will focus on developing a multidisciplinary, integrated program that will build linkages between exposure, dose, effect and risk assessment methods to provide the scientific basis for harmonizing risk assessment approaches, predicting aggregate and cumulative risk, and protecting susceptible subpopulations. In addition, ORD will develop an integrated research program utilizing its intramural scientific capacity in conjunction with extramural grants, cooperative agreements, and interagency agreements. Efforts have been and will continue to be made to identify and foster collaboration with other Federal and State agencies, as well as academic and private organizations having research programs that complement ORD's research efforts.

Research to Improve the Scientific Foundation of Human Health Risk Assessment

ORD's human health risk assessment program is based on the assumption that major uncertainties in risk assessment can be reduced by understanding and elucidating the fundamental determinants of exposure and dose and the basic biological changes that follow exposure to pollutants leading to a toxic response. Research in this area will provide the scientific knowledge and principles to improve the risk assessment of all human health endpoints, aggregate and cumulative risk, and risk to susceptible populations.

Harmonizing Risk Assessment Approaches

ORD's research in this area will address the disparate approach for the risk assessment of cancer and noncancer endpoints. Research on harmonizing risk assessment approaches will lead to a common set of principles and guidelines for drawing inferences about risk based on mechanistic information. The overall goal of this research is that Program and Regional Office risk assessors will use mechanistic data in a harmonized manner for risk assessments for all health endpoints. Specific research objectives include the following:

- -Develop emerging technologies or methods to study mode or mechanism of action;
- -Provide a framework for defining mode or mechanism of action, including understanding the biological events that precede toxic or adverse effects and identifying common or similar modes of action across cancer and noncancer endpoints that could provide the basis for a harmonized approach for risk assessment;
- -Develop a basis for comparing risk across all health endpoints using mechanistic information;
- -Develop principles for the use of mechanistic data to select the most appropriate risk assessment model; and
- -Develop principles for the use of mechanistic data to reduce or replace uncertainty factors in risk assessments, especially for inter- and intraspecies extrapolation, including approaches for linking dosimetry models, such as pharmacokinetic models, with empirical or pharmacodynamic models for effects of pollutants with similar or different modes of action.

Aggregate and Cumulative Risk

ORD's research program on aggregate and cumulative risk will address the fact that humans are exposed to mixtures of pollutants from multiple sources. Research will provide the scientific support for decisions concerning exposure to a pollutant by multiple routes of exposure or to multiple pollutants having a similar mode of action. ORD will also develop approaches to

study how people and communities are affected following exposure to multiple pollutants that may interact with other environmental stressors. Specific research objectives include the following:

-Determine the best and most cost-effective ways to measure human exposures in all relevant media, including pathway-specific measures of multimedia human exposures to environmental contaminants across a variety of relevant microenvironments and exposure durations and conditions;

-Develop exposure models and methods suitable for the EPA and the public to assess aggregate and cumulative risk, including mathematical and statistical relationships among sources of environmental contaminants, their environmental fate, and pathway-specific concentrations; models linking dose and exposure from biomarker data; and approaches to assess population-based cumulative risk, including those involving exposure to stressors other than pollutants; and

-Provide the scientific basis to predict the interactive effects of pollutants in mixtures and the most appropriate approaches for combining effects and risks from pollutant mixtures.

Susceptible and Highly-Exposed Subpopulations

ORD research on susceptible subpopulations will focus on developing a scientific understanding of the biological basis for differing responsiveness of subpopulations within the general population, including factors associated with their differential exposure. Research on biological susceptibility will focus on the role of intrinsic factors, such as life stage and genetic background, and extrinsic factors, such as preexisting disease, on responsiveness to environmental pollutants. Specific research objectives include the following:

-Identify the key factors that contribute to variability in human exposure, including the distribution of human exposures and behavior associated with exposure to pollutants;

-Improve the accuracy of dose estimation in the general population;

-Identify the biological basis underlying differential responsiveness of sensitive subpopulations of humans to pollutant exposure;

-Determine how exposure, dose and effect information can be incorporated into risk assessment methods to account for interindividual variability.

Research to Enable Evaluation of Public Health Outcomes from Risk Management Actions

Generally, the EPA has not prepared retrospective evaluations to determine if the intended benefits in protecting public health were realized once an EPA decision had been in place for a period of time. With the advent of the Government Performance and Results Act (GPRA) and calls for the EPA to stress and demonstrate outcome-oriented goals and measures of success, research is needed to enable evaluation of actual public health outcomes from risk management actions. Estimating public health benefits of EPA regulatory decisions and rule making, or in a more general sense evaluating public health outcomes from risk management actions, will be a challenging undertaking. It will involve a number of disciplines grounded in both the physical and social sciences, and increasingly must take into account the economic and behavioral aspects of human decision-making.

The long term goal of ORD's research on public health outcomes will be to provide the scientific understanding and tools to the EPA and others in evaluating the effectiveness of public health outcomes resulting from risk management actions. Research will focus on identifying, discovering, or developing the most effective methods and models; determining how they can be integrated into a decision-making framework to assist Federal, State, and local decision-makers in evaluating changes in public health as a result of risk management actions; and developing a framework to quantify such changes accurately. Specific research objectives include the following:

-Establish the linkage between sources, environmental concentrations, exposure, adverse effects or disease, and effectiveness such that a change in a human health outcome consequent to a risk management action can be determined by measuring or modeling any one of these linked steps; and

-Improve methods and models by which others can measure or model changes in public health outcomes following various risk management actions.

Because of the novelty of the long term goal and research objectives, and the requirement for an unusually high degree of interdisciplinary coordination, ORD will develop a Multiyear implementation plan for the public health outcomes research program. This plan will provide considerable details on the development, investigation, and delivery phases of the research.

1. INTRODUCTION

The mission of the U.S. Environmental Protection Agency (EPA) is to protect public health and safeguard the natural environment (i.e., air, water, and land) upon which life depends. Risk assessment is an integral part of this mission in that it identifies and characterizes environmentally related health problems. The EPA's Office of Research and Development (ORD) conducts research that contributes to the scientific foundation for risk assessment and risk management decisions in EPA's regulatory programs. Since 1996, ORD has used a risk-based strategic planning process in consultation with EPA's Program and Regional Offices and the external scientific community to set research priorities. From this process, research to improve human health risk assessment was identified as one of six priority research areas in the *1997 Update to ORD's Strategic Plan* (U.S. EPA, 1997a) and *ORD Strategic Plan* (U.S. EPA, 2001b). As such, fundamental human health research is also part of the ORD Sound Science Program under Goal 8, which is one of EPA's ten strategic environmental goals in accordance with the requirements of the Government Performance and Results Act (GPRA) (see text box).

> **Goal 8: Sound Science, Improved Understanding of Environmental Risk, and Greater Innovation to Address Environmental Problems**- *EPA will develop and apply the best available science for addressing current and future environmental hazards as well as new approaches toward improving environmental protection.*

1.1. PURPOSE OF THE STRATEGY

This document, the *Human Health Research Strategy*, presents a conceptual framework of ORD's future research directions in human health risk assessment and risk management. This strategy identifies the broad, overarching questions that will guide ORD's core human health research program over the next 5 to10 years. Core research aims to provide broad, fundamental scientific information that will improve understanding of problem-driven human health issues arising from risk assessment in EPA's Program and Regional Offices. Core research consists of

understanding the fundamental processes that underlie environmentally related health problems; the development of broadly applicable research and risk assessment tools and approaches; and the design, implementation, and maintenance of appropriate measures of environmental exposure (NRC, 1997). Approximately 40% of ORD's research program has been defined as core research. Problem-driven human health issues associated with specific contaminants, media, or issues (e.g., particulate matter, arsenic in drinking water, disinfectant by-products, endocrine disruptors) are addressed in separate ORD Research Strategies and Plans (see Appendix A). Fundamental research issues that cut across those research strategies must often be addressed before more problem-driven questions can be studied. There will be an on-going need to integrate problem-driven and core research as illustrated in Figure 1-1. For example, problem-driven research is being done to study the interaction of pesticides in mixtures because the Food Quality Protection Act (FQPA) indicates that the EPA should consider the risk associated with cumulative exposures of pesticides having a common mechanism. However, core or basic research on the mode or mechanism of action of these pollutants will have to be done before addressing more problem-driven questions concerning the interaction of pesticides based on their mechanism or mode of action.

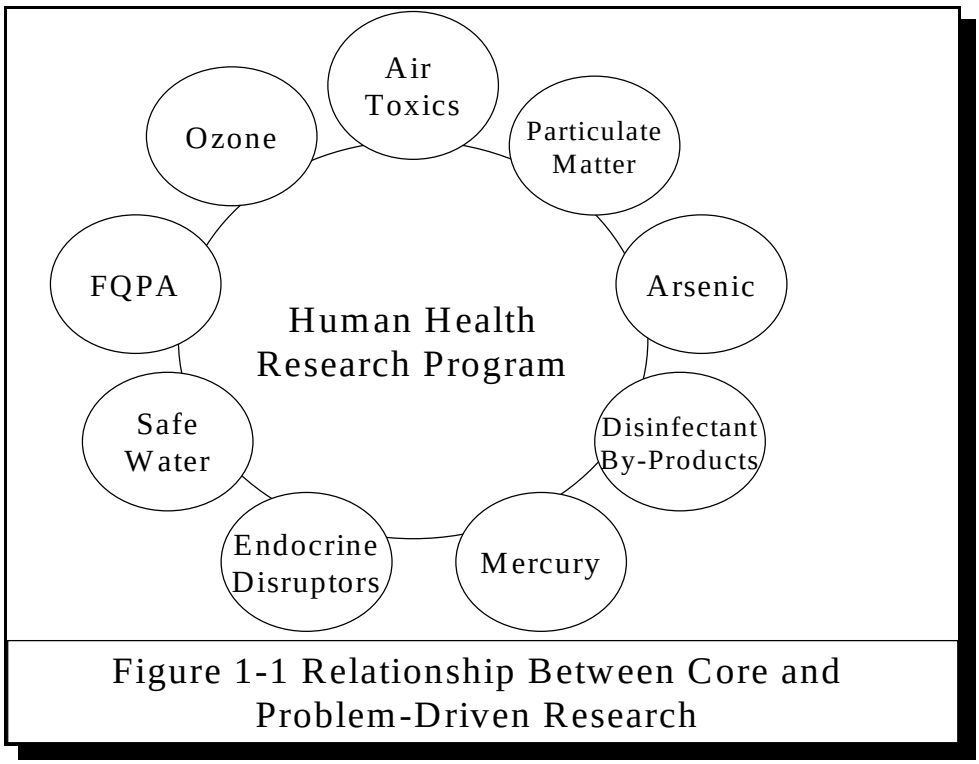


Figure 1-1 Relationship Between Core and Problem-Driven Research

The *Human Health Research Strategy* is not intended to be a technical document. The target audience includes EPA and other Federal agency scientists, managers, and policymakers,

as well as the scientific community at large. It describes the scientific uncertainties, objectives and general approaches that will be taken by ORD's core research program on human health. ORD has developed a Multi-year Plan for Human Health Research that describes anticipated goals and measures over a 5 to 10 year period. In addition, each Laboratory and Center within ORD is developing its own approach to link specific projects and tasks to the ORD Multiyear Plan and the themes described in this research strategy document.

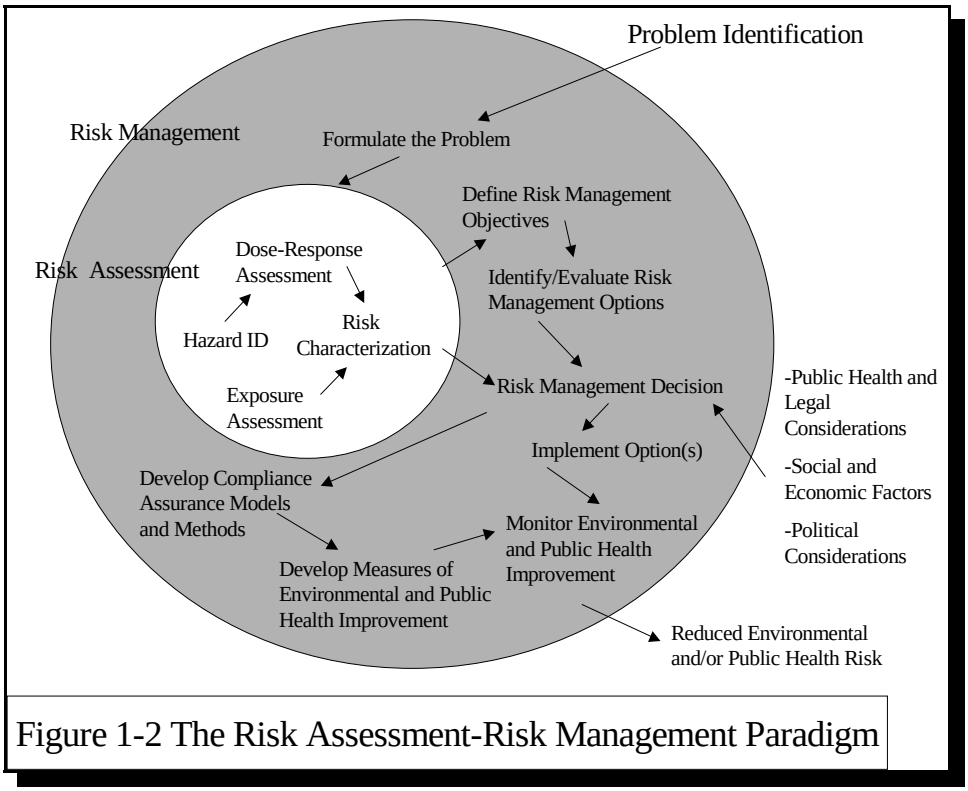


Figure 1-2 The Risk Assessment-Risk Management Paradigm

1.2 CURRENT RESEARCH PROGRAM ON HUMAN HEALTH

Human health risk assessment provides a qualitative and quantitative characterization of the relationship between environmental exposures and effects observed in exposed individuals. In 1983, the National Research Council (NRC) described four primary steps in the process of risk assessment, i.e., hazard identification, dose-response assessment, exposure assessment, and risk characterization (Figure 1-2). Risk assessment is the primary scientific input to the risk management process, which involves the recognition of a potential new risk and development, selection and implementation of EPA actions to address the risk. Risk management often considers a wide variety of other factors. The overall process of risk assessment and risk management is often called the Risk Assessment-Risk Management Paradigm.

Over the last several years, ORD has aligned its organizational structure and research program to be consistent with the Risk Assessment-Risk Management paradigm (Appendix B)(see text box). ORD is organized into three national Laboratories and two Centers. The National Exposure Research Laboratory (NERL) focuses on measuring exposures and producing scientifically defensible exposure models that reduce the gaps in scientific knowledge related to actual human exposure to pollutants. In 1995, the EPA's Science Advisory Board (SAB) (U.S. EPA, 1995) reviewed the state of exposure assessment science and reported that this area was hampered by a variety of technical limitations, including lack of exposure measurement techniques, a paucity of exposure databases and other exposure-relevant data, and reliance on numerous default assumptions with little justification for their selection. The SAB also found that available exposure models had rarely been evaluated against actual human exposure measurements. In addition, there were no comprehensive human exposure models that could describe the complex relationships between pollutant sources, environmental concentrations, exposure pathways, actual human exposures, and the dose that results from exposure to pollutants by multiple pathways. The SAB also found that the methods available for both human exposure measurements and exposure modeling were too intrusive or costly to implement routinely. Much of the work conducted by NERL over the last several years has been directed at these data and methodological gaps.

Laboratories and Centers in ORD

Major Focus	Lab/Center
Exposure and Dose	NERL
Dose and Effects	NHEERL
Risk Assessment	NCEA
Risk Management	NRMRL
Extramural Research	NCER

In the Risk Assessment-Risk Management paradigm, dose-response assessment is the process for determining the likelihood of an adverse effect at a particular exposure or dose. A primary concern for dose-response assessment is an understanding of the dose of the pollutant that reaches its target organ, tissue, cell, or biomolecule. Research on issues related to dose is largely conducted at NERL and the National Health and Environmental Effects Research Laboratory (NHEERL). Research at NERL focuses on pharmacokinetic (PK) modeling to estimate internal dose metrics for multiroute aggregate exposure. Research at NHEERL focuses on determining the basis for metabolic differences between species. This information is crucial

for extrapolating toxicological data from animals to humans in risk assessment and determining the biologically effective dose of the parent compound or metabolite(s) of the pollutant.

The goal of hazard identification is to describe and ultimately predict in humans the toxicological effects of pollutants that might occur due to exposure to environmental agents. Research related to hazard identification is largely conducted at NHEERL and focuses on test methods development and characterization of hazard potential in animal models. Clinical or epidemiological studies are also used to identify potential risks in the human population and generate testable hypothesis for future studies in animal or *in vitro* models. Risk assessment is often confounded by a number of uncertainties related to the risk assessment methodology, including extrapolation across species, extrapolation from short-term to lifetime exposures, and variability of response within the human population. A significant component of research at NHEERL focuses on reducing or eliminating uncertainties in the risk assessment process. Research at NHEERL also seeks to understand the cascade of events between the presence of a pollutant at a target site and the ultimate manifestation of toxicity. Knowledge of the sequence of biological events that must occur to produce an adverse effect [i.e., the mechanism of action, or an understanding of some, but not all, of the key biological steps leading to toxicity, i.e., the mode of action (U.S. EPA, 1996; U.S. EPA, 1999a; IPCS, 1999; Schlosser and Bodganffy, 1999)], is being used with increasing frequency in risk assessment (see Appendix C). Procedures for the use of mechanistic data are defined in the EPA's draft Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999a).

The National Center for Environmental Assessment (NCEA) performs complex risk assessments of national interest and develops risk assessment methods, databases, and tools based on results produced by ORD and others. NCEA also serves an integrating function within ORD, bringing together results from hazard identification, dose-response assessment, and exposure assessment on issues related to the risk assessment process. The risk assessment program includes development of dose-response and exposure models, factors, databases and guidance for conducting risk assessment. Issues confronting the risk assessment program include how to use exposure, pharmacokinetic, and mechanistic data in risk assessment, harmonize

cancer and noncancer risk assessment methods, and conduct cumulative risk assessments of multiple pollutants.

The National Risk Management Research Laboratory (NRMRL) focuses on providing the most effective and useful risk management options and increasing better linkage between risk assessment and risk management efforts.

Intramural research conducted by NERL, NHEERL, NCEA, and NRMRL is complemented by extramural research sponsored by ORD's National Center for Environmental Research (NCER). Through the Science to Achieve Results (STAR) Program, NCER supports grants that focus on specific research needs consistent with the mission of the EPA. For example, the STAR Program provides support to extramural scientists to develop statistical and predictive approaches for assessing risks from pollutant mixtures. Other examples of STAR research include 12 EPA/National Institute of Environmental Health Sciences (NIEHS)-supported Centers for Children's Health and Disease Prevention Research and individual studies, such as the development of biomarkers for risk assessment in children.

1.3 FUTURE RESEARCH PRIORITIES

1.3.1 Framework for an Integrated Research Program in ORD

ORD will develop a multidisciplinary research program that addresses linkages lying along a continuum from the source of an agent through exposure and dose to adverse outcome such as disease (Figure 1-3). One example of the need for an integrated research program arises from the opportunities and challenges associated with the data contained in the recently released Center for Disease Control and Prevention's (CDC) National Report on Human Exposure to Environmental Chemicals. This report contains blood and urinary values on 27 pollutants collected as part of the National Health and Nutrition Examination Survey (NHANES). CDC anticipates this list growing to at least 100 pollutants over the next 3 to 4 years. However, these "biomarker" values alone yield little insight as to the risk encountered by the general population or susceptible subpopulations or the major contributing pathways so as to direct risk management

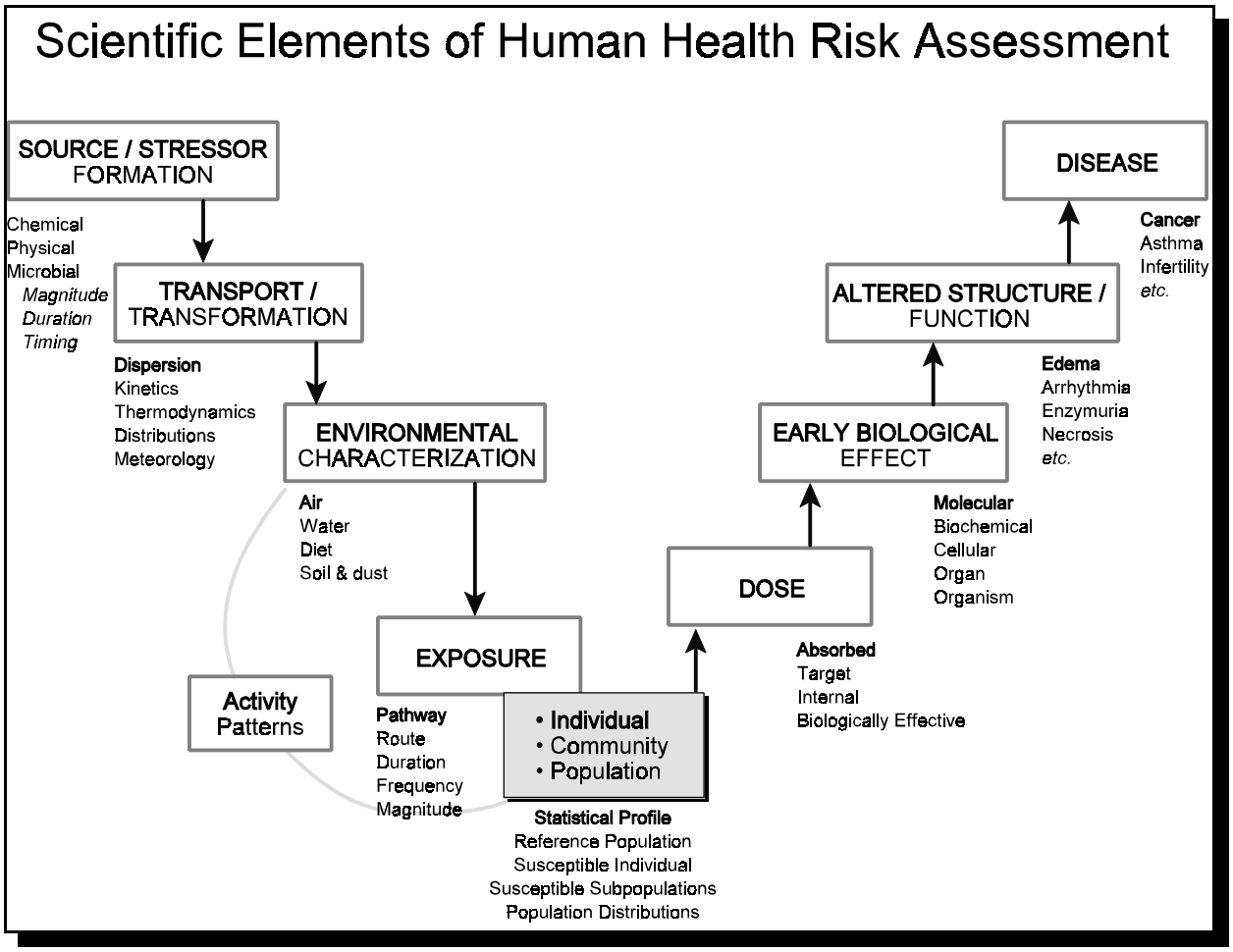


Figure 1-3 The Exposure-Dose-Effect Continuum

efforts. By focusing on the linkages between dose, as evidenced by biological markers such as those reported in the CDC report, and measures of exposure, early biological effect, altered structure or function and disease, ORD will provide critical insights needed to interpret these emerging biomonitoring data.

ORD's evolving integrated approach to problem formulation and research planning is illustrated in Figure 1-4. Risk assessment issues arising from Regional or Program Offices, through legislative or regulatory mandates, or ORD research results will be evaluated to determine the scientific questions (Figure 1-4, Box A). This evaluation will lead to the design of studies to address those uncertainties (Box B). Results from these studies (Box C) will be used

to refine additional studies and/or used to generate models (Box D) to inform the development of better risk assessment methods. Efforts to construct modules or compartments of models (Box D) will feedback onto the design and execution of additional experiments.

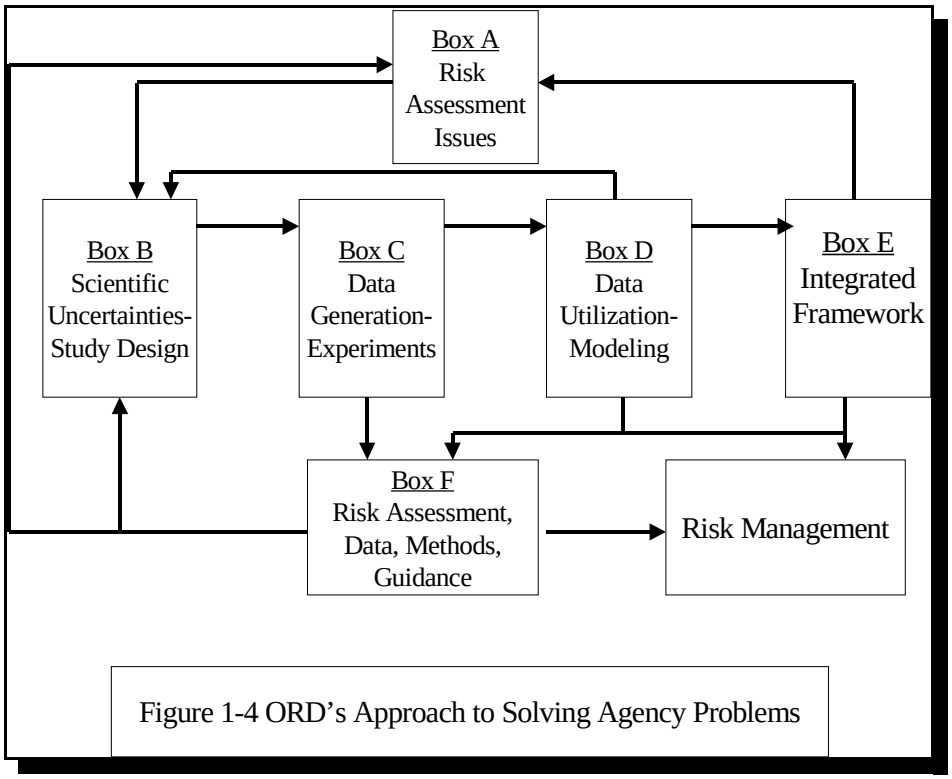


Figure 1-4 ORD's Approach to Solving Agency Problems

Ultimately, results from all experiments and models will be used to develop risk assessment methods (Box F) and develop an integrated framework (Box E) that will form the scientific basis for risk assessment guidance and risk management decisions. Consolidated information resulting from the integrated framework may also be used to inform or redefine the original risk assessment issue.

A conceptual model illustrating a completely integrated research program is illustrated in Figure 1-5. As this figure shows, analysis of risk assessment issues gives rise to scientific questions concerning exposure, dose, effects, and risk assessment methods. For example, risk assessment questions related to exposure might require studies involving the development of analytic methods and the execution of pilot-scale laboratory or field exposure research followed by larger scale population or epidemiological studies to gain important exposure and/or exposure factor data. The results of this research could be used to help develop exposure assessment models. Research questions related to dose might involve experiments to develop analytical methods, obtain pharmacokinetic data, or identify biomarkers. The results of these experiments would be used to develop physiologically-based, pharmacokinetic models for estimating internal

dose. Effects research may require the development of sensitive and specific methods to help understand the biological substrates underlying the mode or mechanism of action of environmentally relevant pollutants.

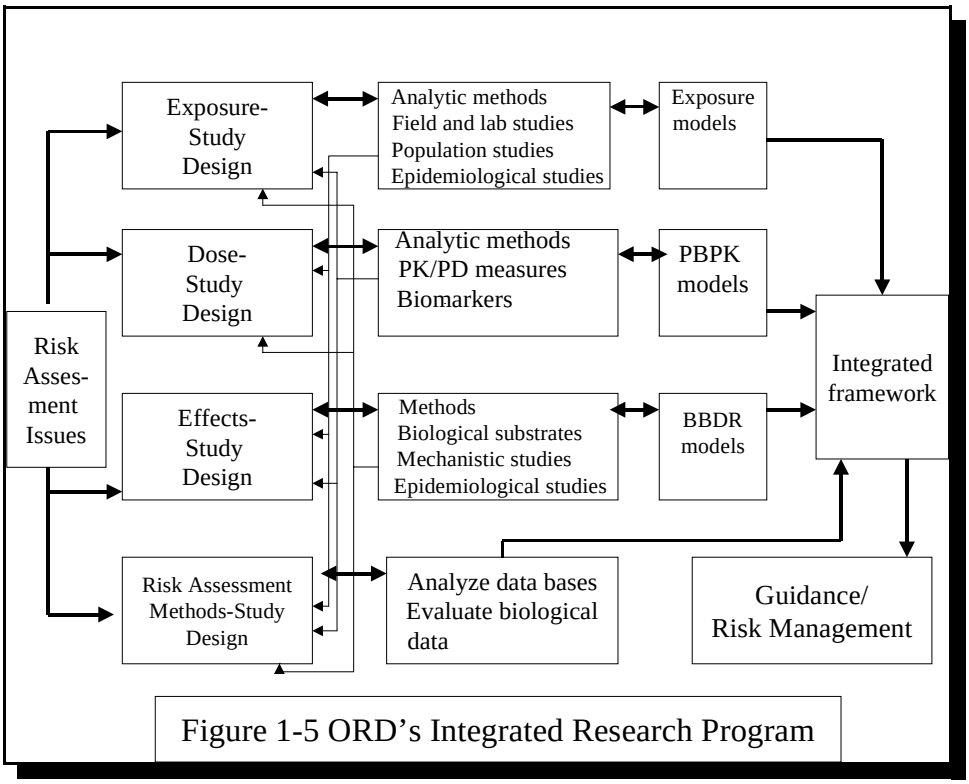


Figure 1-5 ORD's Integrated Research Program

Epidemiological studies may provide the basis for confirming possible health-related adverse effects in the human population and generate testable hypotheses for subsequent confirmation in animal or *in vitro* models. The results of effects research would be used to develop biologically based dose-response models linking effects observed at the cellular or molecular level to adverse health effects. Assessment of data generated from exposure, dose and effects research would be used to formulate better risk assessment methods. All of the data generated from research on exposure, dose, effects, and risk assessment methods would be used to help develop an integrated framework for the development of guidance for risk assessment and scientific support for risk management options.

Figure 1-5 also shows that results from various experiments and models may feed back at any time through an iterative process to help the design of future experiments. Results from experiments and outputs from models in any area of analysis (i.e., exposure, dose, effect, risk assessment) may influence the design of studies and generation of data in other areas. For example, the results of field studies concerning exposure of children to pesticides might influence the choice of dose or concentration of pollutants for future research.

ORD 's ongoing research on asthma and exposure of children to fungi and molds serves as a specific example of a multidisciplinary, integrated research program that uses the scientific expertise and resources from the various ORD Laboratories and Centers to address a high priority research issue (Figure 1-6). In 1998, a team of researchers from NERL, NHEERL, NCEA and NRMRL was organized to address the effects of the *S. chartarum* fungus, a common indoor contaminant, on children's health. The first objective of this program was to determine before and after remediation, the quantities of S. *chartarum* spores in dust from homes of children with asthma or pulmonary hemosiderosis and assess specific antibodies to mold proteins in these children. A second objective was to establish a mouse model of allergic lung disease to characterize IgE-inducing proteins from three fungi, including S. *chartarum*, immunologically and, by advanced proteomics, identify any common characteristics. This research addresses the hypothesis that differences in protein constituents of mold are associated with allergenicity. The third objective of this research program is to demonstrate parallels between human and rodent responses to the mold in order to facilitate interspecies extrapolation. Epidemiological and clinical studies evaluate the exposures of children to fungi that might lead to asthma using a cohort of children to addresses the hypothesis that participants in the fungal exposed cohort will have significantly more asthma than control participants. Another objective of this research is to test methods to reduce spore release and growth of fungus and begin to develop a risk assessment model. The ultimate goal is develop a

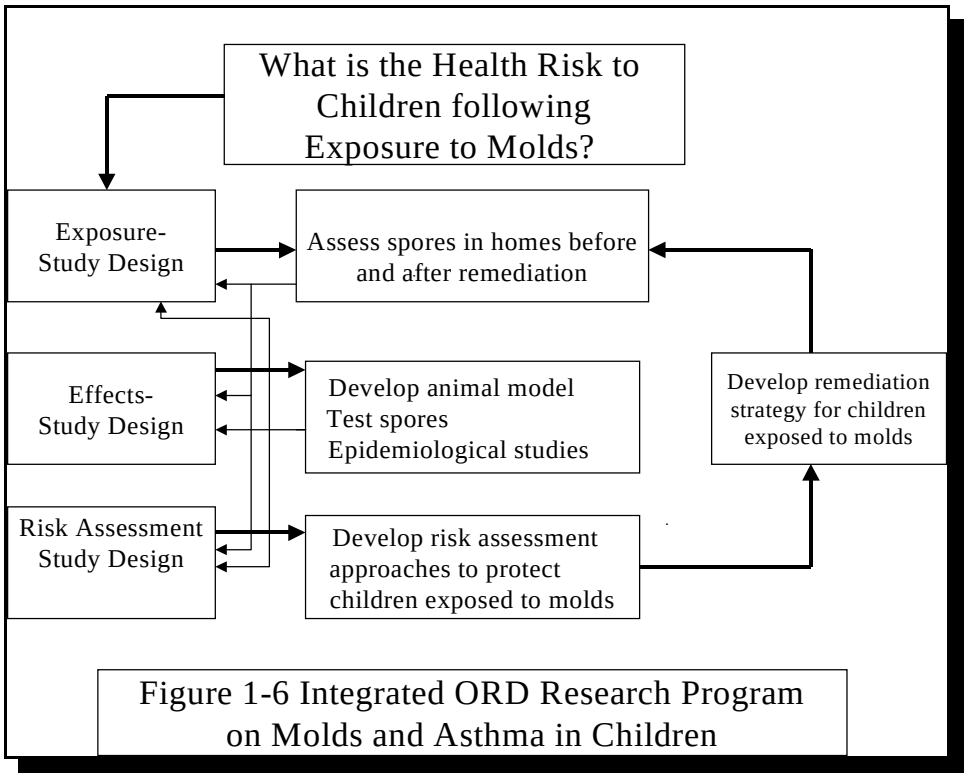


Figure 1-6 Integrated ORD Research Program on Molds and Asthma in Children

model than can be used to address risk assessment and risk management approaches for indoor molds associated with asthma and other health conditions.

Figure 1-6 illustrates the integrated multidisciplinary approach that has been developed to address this high priority need of the EPA. Exposure data from field studies identify and characterize exposures to fungi that might be associated with childhood asthma. These studies also help define the relationship between exposure and effect and provide important exposure information for the design of effects studies and risk assessment approaches. Research on effects focuses on developing animal models of allergic lung disease that can be extrapolated to humans and on studies providing a causal link between the potential mode of action or mechanism and allergic lung disease. Mechanistic effects research helps confirm the associations observed in the exposure assessment and could lead to the identification of specific fungi species involved in producing allergic lung disease. Epidemiological studies in children provide important information for the design of risk assessment approaches to protect children exposed to fungi and help shape the design of future studies. Risk assessment approaches are being developed based on results from the exposure assessment and effects research, all of which provide the scientific basis for development of risk management options and remediation strategies, if necessary. Once a remediation strategy has been implemented, future studies will be designed to evaluate the effectiveness of the strategy. Depending on the outcome of these studies, additional research on exposure, effects and risk assessment models may be initiated to devise a more effective risk assessment-risk management approach.

1.3.2 Research Themes

Based on input from Regional and Program Office risk assessors and ORD scientists, future ORD research will focus on two strategic directions (see text box on next page), including 1) research to improve the scientific foundation of human health risk assessment and 2) research to enable evaluation of public health outcomes from environmental risk management decisions. Research to improve human health risk assessment will emphasize three themes, i.e., harmonizing cancer and noncancer risk assessments, assessing aggregate and cumulative risk, and evaluating risks for susceptible and highly exposed subpopulations. Research on

harmonizing risk assessment addresses the need to develop a consistent approach for the use of mechanistic information in all health risk assessments. Research on assessing aggregate and cumulative risk addresses the need to develop risk assessment/risk management approaches to evaluate multichemical/multipathway exposures to environmental agents, while research on risks to susceptible subpopulations focuses on understanding variability in human responses to environmental agents. Susceptible subpopulations also include populations of people that are differentially exposed to environmental agents. These themes are discussed in greater detail in Chapter 2.

Strategic Research Directions

- ❑ Research to Improve the Scientific Foundation of Human Health Risk Assessment:
  - • Harmonizing Cancer and Noncancer Risk Assessments
  - •Assessing Aggregate and Cumulative Risk
  - •Evaluating the Risk to Susceptible Human Subpopulations
- ❑ Research to Enable Evaluation of Public Health Outcomes from Environmental Risk Management Decisions.

ORD will also initiate research to enable the evaluation of public health outcomes from risk management actions. This program anticipates new EPA efforts to measure and monitor improvements in environmental public health following risk management actions as underscored by requirements that the EPA evaluate the success of its environmental programs and decisions. Success will be measured by changes in health outcomes and indicators resulting from risk management decisions. The EPA has traditionally relied on "process" measures (e.g., decreased emissions, number of sites cleaned up) to measure public health benefit indirectly. ORD's future research program seeks to identify and validate health events that can better serve as true public health outcome measures (Figure 1-7). The regulatory and scientific bases for this part of the research program is described in greater detail in Chapter 3 of this document.

1.4 STRATEGIC PRINCIPLES

The following strategic principles will be used in developing and implementing ORD's research program on human health:

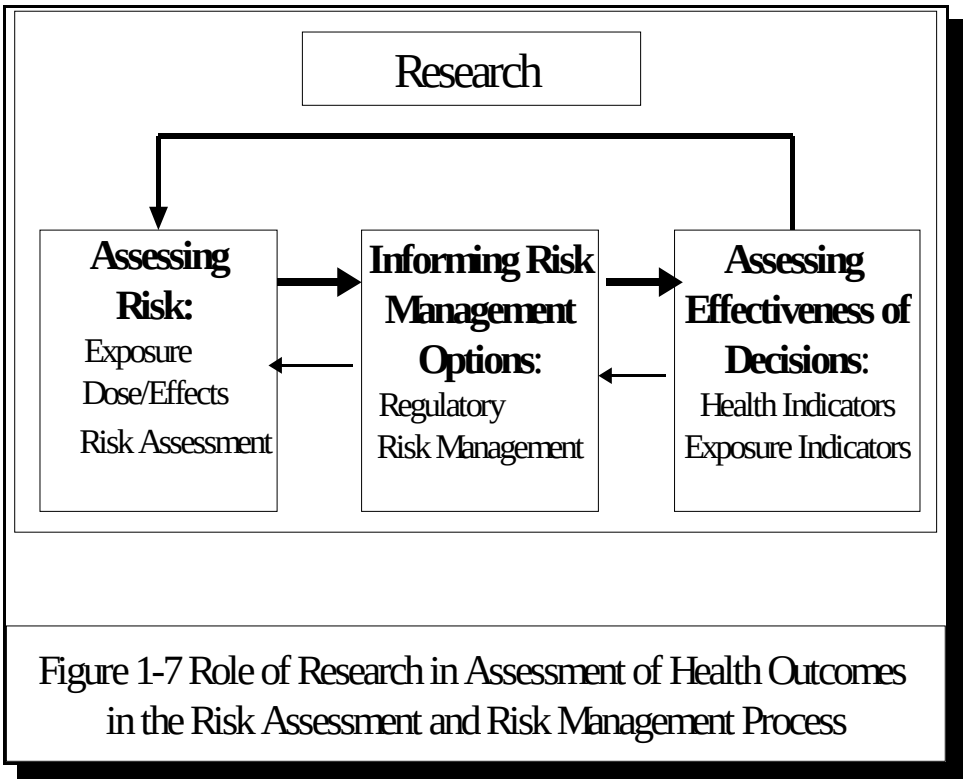


Figure 1-7 Role of Research in Assessment of Health Outcomes in the Risk Assessment and Risk Management Process

Collaboration across ORD- As described previously, the intramural ORD program is organized around the Risk Assessment-Risk Management Paradigm (Figure 1-2), i.e., NERL, NHEERL, NCEA and NRMRL. ORD's future research program will focus on more complex environmental problems requiring collaboration and synergy between the various Laboratories and Centers in ORD. Scientists in Program and Regional Offices are also viewed as collaborators, as well as clients, and collaborative relationships will be established to design and conduct studies related to human health risk assessment and risk management.

Focus and broad application—A research strategy to improve human health risk assessment and management must emphasize selected high-priority issues with outcomes expected to have wide impact on risk assessment. ORD will focus the core human health research program on environmental pollutants, which is consistent with the expertise and infrastructure ORD has developed over the last several years. However, as knowledge gaps are identified for other classes of environmental agents, such as microbes and bioaerosols, research will be initiated to address specific questions related to those agents.

Support EPA's Mission—The research must address knowledge gaps in risk assessment identified by Program and Regional Offices or raised by specific regulatory or legislative requirements. Results should have tangible benefits to all groups interested in improved risk assessments (i.e., States, local governments, industry, nongovernmental environmental organizations, communities, international governments). ORD's research will result in products and information that have direct and practical applications in risk assessment. ORD scientists will also identify issues that may be important to the future of risk assessment that are not major concerns to programs and regions at the present time.

Outreach, coordination, and partnership with external scientific community. ORD will develop an integrated research program utilizing its intramural scientific capacity in conjunction with extramural grants and cooperative and interagency agreements. In addition, efforts have been and will continue to be made to identify and foster collaboration with other Federal and State agencies, as well as academic and private organizations, that complement ORD's research efforts (see Appendix D).

1.5 ORGANIZATION OF THE DOCUMENT

This document includes an executive summary, four chapters, and appendices. This chapter introduces the strategic directions and research priorities for ORD's future core research program in human health. Chapter 2 presents ORD's integrated, multidisciplinary research program to improve the scientific foundation of human health risk assessment for the three priority areas: harmonized risk assessment approaches, aggregate and cumulative risk, and susceptible subpopulations. Chapter 3 describes ORD's proposed research program to evaluate the impact of public health outcomes. Chapter 4 contains the references for this document.

2. RESEARCH TO IMPROVE THE SCIENTIFIC FOUNDATION OF HUMAN HEALTH RISK ASSESSMENT

ORD's human health risk assessment program is based on the assumption that major uncertainties in risk assessment can be reduced by understanding the fundamental principles of how, at what level, and how often humans are exposed to pollutants; how much of the toxic moiety arrives at the target site; and the basic biological changes that lead to a toxic or adverse health effect. Research questions related to harmonizing risk assessment, assessing aggregate and cumulative risk, and evaluating risk to susceptible subpopulations will be framed to address knowledge gaps and interrelationships of events along a continuum from source through exposure and dose to effect (Figure 1-3). The overall objective of ORD's human health research program is to link exposure, dose, and effect approaches along this continuum to provide an integrated information base for scientifically defensible risk assessment and risk management decisions.

2.1 Research on Harmonizing Risk Assessment Approaches

2.1.1 Scientific Uncertainties

Assessment of health risk from exposures to environmental agents has traditionally been performed differently depending on whether the response is a cancer or a noncancer health effect. This practice has been based on a limited understanding of the mode of action of toxic substances. Historically, cancer was thought to be largely the consequence of direct interaction of a carcinogen with DNA to produce a heritable change in a single cell that eventually produced a tumor. It was thought, therefore, that the dose-response for such a mechanism would not show a biological threshold, but would be linear at low doses. This led the EPA to employ a science policy that cancer risk should be estimated by a linear, nonthreshold dose-response method.

On the other hand, a threshold has generally been assumed for noncancer effects, based on considerations of compensatory homeostasis and adaptive mechanisms. The threshold concept assumes that a range of exposures can be tolerated up to some finite level without adverse effects. This threshold will vary from one individual to another, so that there will be a distribution of

thresholds in the population. Except for some pollutants such as the criteria air pollutants, evaluating human risks for noncancer effects has generally involved the determination of a level of daily exposure that is likely to pose no appreciable risk of deleterious effect during a lifetime.

The disparate approach for assessment of cancer and noncancer endpoints has been questioned (e.g., NRC, 1994). It now appears that carcinogens can affect many cellular targets and biochemical and biologic processes that eventually lead to the formation of tumors. Such targets may include DNA, which contains the genes that control cell growth, or biochemical processes involved in cell growth regulation, cell signaling, and cell-to-cell communication. Other mechanisms may involve cell toxicity and death, perturbation of hormonal systems, and suppression of the immune system. Many of these mechanisms may have thresholds of response, as discussed in the proposed new cancer risk assessment guidelines (U.S. EPA, 1996, 1999a). It has also been hypothesized that threshold considerations may not be applicable to all noncancer effects, e.g., lead-induced cognitive deficits in children. Furthermore, our emerging understanding of the mechanisms of carcinogenesis and other health effects suggests that the underlying basis for certain noncancer and cancer endpoints may have common precursors. For example, pollutant-induced toxicity can cause altered biological function, cell death, and tissue regeneration, while surviving cells compensate for that injury by increasing cell proliferation which may result in tumor formation if continued unchecked. Thus, the primary precursor effect may be related to both the cancer outcome and other types of noncancer biological effects.

Understanding an agent's mechanism of action will be crucial to more accurate prediction and characterization of hazard and risk, and will be the basis for developing harmonized approaches for all health endpoints. *Harmonization* in this context refers to the development of a consistent set of principles and guidelines for drawing inferences from scientific information. It does not mean that a single methodology should be used for the assessment of all toxicities and pollutants. Instead, it emphasizes the need for consistent application of all pertinent information on toxicity, dosimetry, mode of action, and exposure in all risk assessments regardless of the nature of toxicities or pollutants. ORD will focus its research to improve the foundation of these risk assessment methods by better understanding the mechanisms or modes of action that are common to cancer and noncancer health effects.

2.1.2 Research Objectives

The following research objectives provide the framework to develop an integrated research program to harmonize risk assessment approaches:

-Develop emerging technologies or methods to study mode or mechanism of action;

-Provide a framework for defining mode or mechanism of action, including understanding the biological events that precede toxic or adverse effects, and identifying common or similar modes of action across cancer and noncancer endpoints that could provide the basis for a harmonized approach for risk assessment;

-Develop a basis for comparing risk across all health endpoints using mechanistic information;

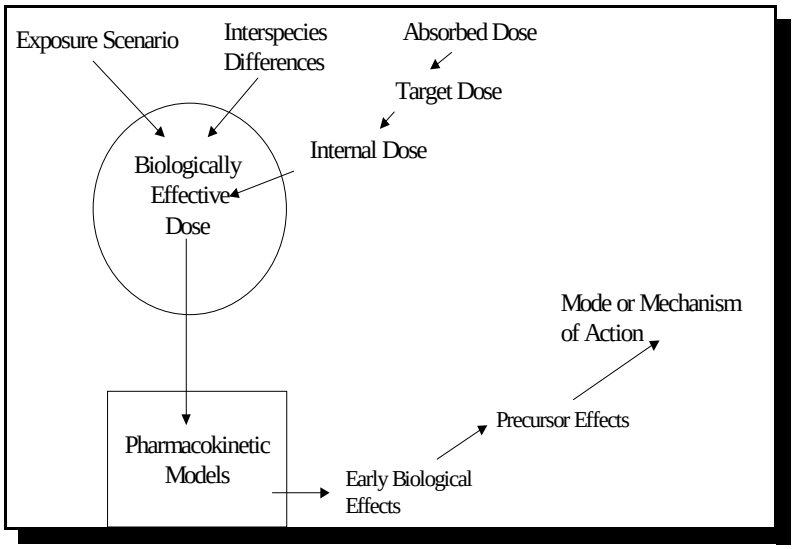
-Develop principles for the use of mechanistic data to select the most appropriate risk assessment models; and

-Develop principles for the use of mechanistic data to reduce or replace uncertainty factors in risk assessments, especially for inter- and intraspecies extrapolation, including approaches for linking dosimetry models, such as pharmacokinetic models, with empirical or pharmacodynamic models for effects of pollutants with similar or different modes of action.

2.1.3 Research Approach

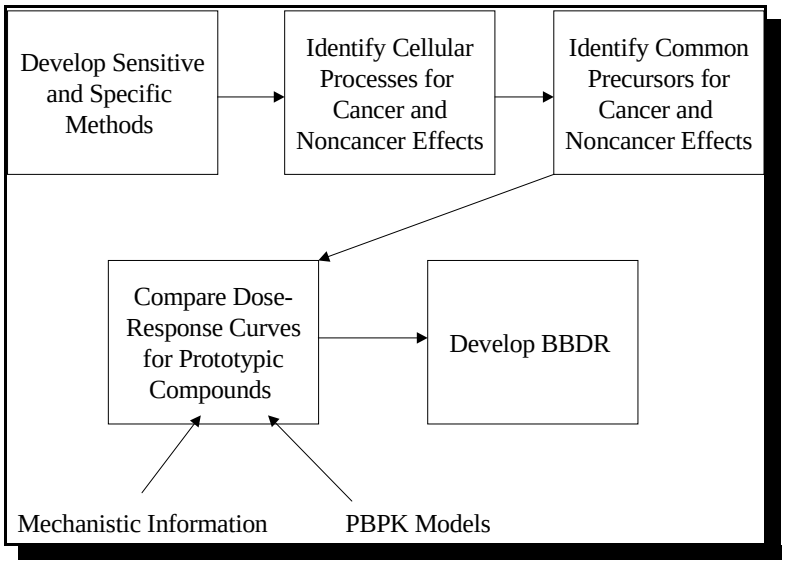
Exposure Research. Specific exposure issues have not been identified within the context of harmonization of risk assessment approaches. Research to characterize the various exposure pathways to relevant pollutants is described in Section 2.2 under the theme of Aggregate and Cumulative Risk and includes describing the magnitude and nature of the pollutants to which people are exposed, as well as the timing and sequence of those exposures. Research on differential exposure of susceptible subpopulations is described in Section 2.3.

Dose Research. It is hypothesized that there may be common biological effects that serve as precursors to various health effects. For example, some pollutants may cause multiple effects, both cancer and noncancer, through initially similar mechanisms such as adduction of DNA or binding to a receptor. Subsequent events must differ in order to produce different effects. Other pollutants cause multiple effects through multiple mechanisms, often through the formation of metabolites with different biological activities. In either case, knowing the biologically effective dose of the active pollutant at the target site is crucial for elucidating mechanisms and modes of cancer and noncancer health effects for risk assessment. Research on dose will identify the biologically effective dose of parent compound or metabolites in target tissue and attempt to relate those levels to the presence of early biological and precursor effects at the molecular, biochemical, cellular, organ and organismal levels (see schematic above). This information will, therefore, be crucial for studies attempting to elucidate mode or mechanism of action. The development of pharmacokinetic models to inform studies on mode or mechanism of action must also take into account variables such as the duration of exposure and possible interspecies differences in sensitivity.



Effects Research. Central to the question of harmonizing risk assessment approaches is whether various modes or mechanisms of action have a similar necessary step (e.g., cell proliferation, receptor interaction, response to injury or stress, alterations in DNA repair mechanisms, apoptosis) leading to the adverse effect. Virtually every toxic event in a tissue or organism exposed to a pollutant is modulated by a finite number of damage- response pathways by which cells sense the status of their internal environment. Through these sensors, critical processes that activate specific genes or proteins to cause the cell to migrate, proliferate, differentiate, or die are made by a cell's biochemical machinery. Progress in this area depends on

a clear understanding of the changes in the biology of the cell following delivery of the active chemical moiety to target cells and the relationship of responses with dose. Determining the presence of the active toxic moiety at specific target sites will be crucial for these studies.



A significant first step in effects research on harmonization will be the development of sensitive and specific methods (see schematic above) to study mechanism or mode of action based on the application of emerging technologies, especially proteomics and genomics. Bioinformatic approaches will also have to be developed to help interpret the meaning of changes coming from multigene, microarray assays used in hazard identification. Effects research will initially focus on identifying cellular processes (e.g., regeneration, proliferation) that may be similar for cancer and noncancer health effects, which will lead to studies that will identify common biochemical or molecular pathways associated with those cellular processes. This research will then focus on studies concerning the effects of environmentally relevant doses or concentrations of prototypic pollutants with similar putative modes or mechanisms of action, or pollutants sharing similar structure-activity relationships. If a common cellular target can be identified for specific adverse outcomes, PBPK models will determine target tissue levels and the influence of duration of exposure and interspecies variation on adverse effects. ORD's effects research will lead to BBDR models that take into account the sequence of early biological events leading to adversity (i.e., mechanisms or modes of action) for multiple endpoints, the shape of the dose-response curves at low doses, and the influence of interspecies differences.

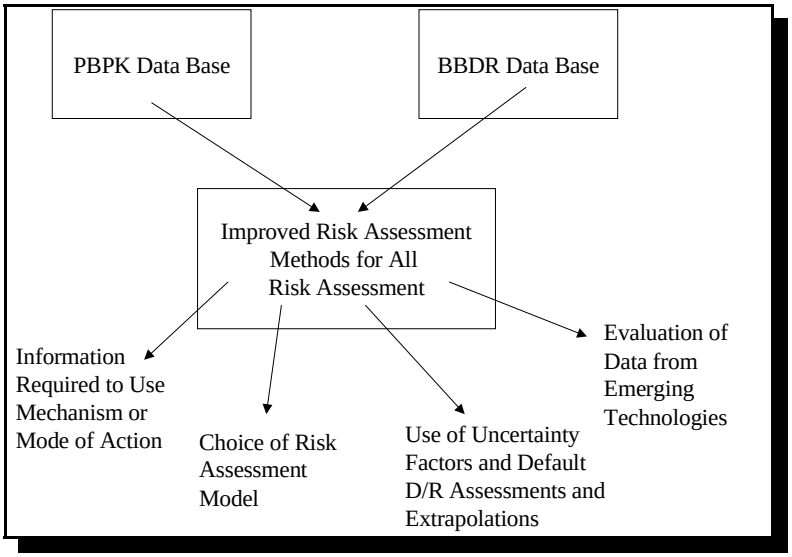
Computational Toxicology

Integrates computing and information technology with molecular biology to improve EPA's prioritization of data requirements and risk assessment of toxic chemicals

Mechanistic effects research based on emerging technologies such as proteomics, genomics and bioinformatics will also feed directly into ORD's efforts to set mechanistically based priorities for pollutant risk assessments and optimize *in vivo* and *in vitro* testing requirements through the use of *in silico* methods and molecular profiling, i.e., computational toxicology (see text box). For example, *in silico* methods, such as quantitative structure activity relationships (QSAR), could be used to determine which set of chemicals out of a larger population (e.g., TSCA inventory) might have the potential to produce an adverse effect (e.g., cancer or reproductive toxicity). This information could be used to prioritize subsequent testing of this subset of chemicals for potential human health or environmental effects. Emerging technologies such as genomics and proteomics could be used to generate molecular profiles that would serve as diagnostic tools to discriminate toxicological pathways leading to different adverse effects. Diagnostic tools could be used to design *in vitro* and *in vivo* tests to confirm the toxicological pathway involved in producing the adverse effects. This information would then be used to guide the selection of specific testing protocols for risk assessment. ORD will initially demonstrate the feasibility of this approach by focusing on prioritization and screening assays and models for endocrine disrupting chemicals. This class of pollutants was chosen as a basis for a proof-of-concept approach because ORD has considerable experience in determining environmental exposure levels to these chemicals, as well as developing *in vivo* and *in vitro* tests in response to provisions of the Food Quality Protection Act.

Risk Assessment Methods. In developing harmonized approaches for the assessment of risk to different health endpoints, a key issue is to determine how much information is needed to show that a particular toxic effect is mediated by a specific mode of action and that the pollutant or its metabolite is present in sufficient quantities in the target tissue (see schematic on next page). For example, the proposed cancer risk assessment guidelines (U.S. EPA, 1999a, 1996) provide for judging the plausibility and adequacy of available evidence for a postulated mode of action, identifying susceptible subpopulations, and determining the most appropriate approaches and

methods for low-dose extrapolation. ORD research on risk assessment methods will focus on how to incorporate mode-of-action information for other health endpoints. Guidance will also be developed to determine how different endpoints of toxicity could develop through common biological processes or modes of action. One high priority for ORD research on risk assessment methods will be prototype assessments for both data-rich and data-poor pollutants to illustrate how mode of action, physiologically based pharmacokinetic (PBPK), and biologically based dose response (BBDR) models may be used *in lieu* of default approaches. Risk assessment research is also needed to develop principles to evaluate the results of studies in which the data have been generated using genomic or proteomic methods. This "translational" research will be a major challenge for the EPA as the onslaught of data generated by these new approaches will far outpace the research and guidance on interpretation and application in risk assessment.



Recent EPA guidance to improve risk assessments has emphasized the importance of providing risk managers with a fuller characterization of risk. Current default approaches to express risk for health effects presumed to be mediated by threshold or nonlinear modes of action include the use of reference toxicity values (e.g., chronic oral RfD, inhalation RfC) or the concept of the margin of exposure (MOE)(i.e., the ratio of the critical NOAEL to the expected human exposure level). Although these risk assessment models consider all the available data, they do not provide an explicit estimate of variability and uncertainty or provide information on the consequences of exposures that exceed the reference values or have a small MOE.

An important focus of ORD's risk assessment research on harmonization will be the development of approaches to characterize variability and uncertainty in reference toxicity values

and to provide a probabilistic framework for estimating risks associated with exposures above reference toxicity values. This research will examine data underlying the various uncertainty factors commonly applied in setting reference values, including factors for interspecies and intraspecies extrapolation (including pharmacokinetic and pharmacodynamic variability) and variability in responses due to changes in exposure duration. The goal will be to develop probability distributions that can be combined to characterize the variability and uncertainty around the reference values for health effects. Various statistical approaches, including the use of categorical regression, will be explored as a means for estimating risks above the reference toxicity values for informing risk management decisions and supporting economic benefits analyses. Risk assessment methods on risk predictive models for cancer and noncancer effects will also be investigated.

2.2 Research on Aggregate and Cumulative Risk

2.2.1 Scientific Uncertainties

The development of risk assessment methodology during the 1970s and early 1980s closely followed the EPA's strategy for pollution control. Historically, the EPA evaluated the risks of a single pollutant in a single exposure medium, such as lead in outdoor air or drinking water. In reality, people are constantly exposed to mixtures of pollutants. Furthermore, exposure to the same pollutant may occur from a variety of routes, including the air, water, and food. In addition, the composition and concentration of pollutants in the environment is constantly changing, depending on people's activities and geographical location. It is now fully understood that environmental exposure to pollutants occurs via multiple exposure routes and pathways, including inhalation, ingestion, and uptake through the skin. Research on aggregate and cumulative risk will focus on defining the multitude of ways in which people are exposed to pollutants and characterizing the subsequent effects and risks.

The FQPA directed the EPA to include in its assessment of pesticide safety the risk associated with the cumulative effects of chemicals that have a common mechanism of toxicity, and to consider aggregate dietary and non-occupational sources of pesticide exposure. However, the EPA's efforts to assess aggregate and cumulative risk go far beyond the FQPA and pesticides. For example, the Office of Water must assess risks from mixtures of disinfectants and their byproducts, and must balance those risks against the risks of toxic microbes in the drinking water supply. The Air Program needs methods to assess risks from mixtures of criteria air pollutants and sources containing a mixture of hazardous air pollutants. The Waste Program deals with mixtures of many different chemical classes found together in the soil, water, and air of waste sites and their surroundings. In addition, the EPA's Program and Regional Offices deal with communities that may be more highly exposed than average and subject to a variety of other stressors such as poverty, lack of access to medical care, inadequate nutrition, and stresses associated with living near landfills, incinerators, and/or heavy industry. To encompass all these concerns, this document defines aggregate exposure and cumulative risk broadly, in accordance with the working definitions developed by the EPA's Science Policy Council (see text box above).

Working Definitions Developed by EPA Science Policy Council

Aggregate Exposure: The combined exposure of an individual or defined population to a specific agent or stressor via relevant routes, pathways, and sources.

Aggregate Risk: The risk resulting from aggregate exposure to a single agent or stressor.

Cumulative Risk: The combined risks from aggregate exposures to multiple agents or stressors.

The traditional approach to assessing aggregate and cumulative risk is to focus primarily on individual pollutants and their sources. The pollutants are initially traced through the environment and the concentrations and doses of each chemical are estimated separately. The toxicity and risks from the multiple stressors are added or combined, using the basic methods in EPA's *Chemical Mixtures Guidelines* (U.S. EPA, 1986, 2000c) to determine risk. This pollutant-based approach has most often been applied for estimating exposures and risks for specific locations or scenarios (*e.g.*, risks associated with a hazardous waste site).

The objective of ORD's research program on aggregate and cumulative risk is to provide methods, models, data, and guidance for assessing human health risk so that the EPA can protect the health of the public and environment more effectively. ORD's research program on aggregate and cumulative risk will take two approaches, i.e., chemical-focused and population-based. The chemical-focused approach may be better suited to address the likely impacts of a specific source or a pollution control strategy when the key variables associated with that source can be well characterized for specified human exposure scenarios. A population-based approach may be better at revealing total exposures and identifying when important sources or important pathways of exposure may not have been identified. A population-based approach may also be useful in assessing public health outcomes, because the objective of any control policy is to decrease public exposure and risk. ORD research will build on these two approaches to develop scientifically robust aggregate and cumulative risk assessment methods, including how to identify important stressors to a population, combine risk over several stressors, define risks that accumulate over time, and assess the interaction between stressors. The research program for aggregate and cumulative research consists of several interrelated research efforts, all of which add critical components to the overall aggregate/cumulative risk assessment effort.

2.2.2 Research Objectives

The following research objectives provide the framework to develop an integrated research program on aggregate exposure and cumulative risk:

- -Determine the best and most cost-effective ways to measure human exposures in all relevant media, including pathway-specific measures of multimedia human exposures to environmental contaminants across a variety of relevant microenvironments and exposure durations and conditions;
- -Develop exposure models and methods suitable for the EPA and the public to assess aggregate and cumulative risk, including mathematical and statistical relationships among sources of environmental contaminants, their environmental fate, and pathway-specific concentrations; models linking dose and exposure from biomarker data; and

approaches to assess population-based cumulative risk, including those involving exposure to stressors other than pollutants; and

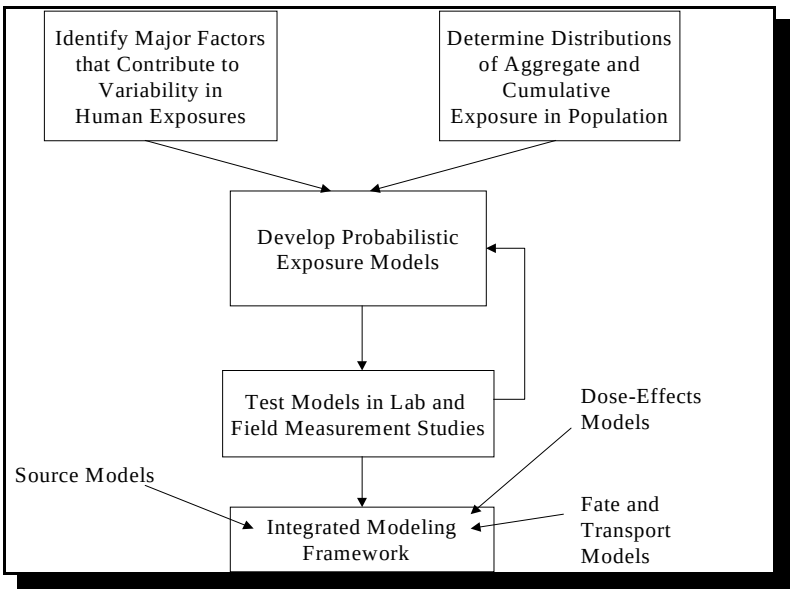
-Provide the scientific basis to predict the interactive effects of pollutants in mixtures and the most appropriate approaches for combining effects and risks from pollutant mixtures.

2.2.3 Research Approach

Exposure Research. One goal of ORD's research program is to develop methods and approaches for measuring exposures and identify exposure factors accounting for aggregate and cumulative exposure. In assessing aggregate and cumulative risk, the focus will be on measuring exposure and estimating biologically relevant dose in exposed individuals. Considerable progress has been made over the past two decades toward developing personal measurement-based methodologies for assessing human exposures, in either a population of concern, or in the population at large. The Total Exposure Assessment Methodology program and the National Human Exposure Assessment Survey (U.S. EPA, 1999b) have demonstrated the techniques and values of measuring personal exposures. In addition, the CDC continues to improve their methods for measuring pollutants and their metabolites in blood and urine and have recently begun reporting exposure data for a representative sample of the U.S. population. These measurement-based methods add to our arsenal of approaches to address aggregate and cumulative risk.

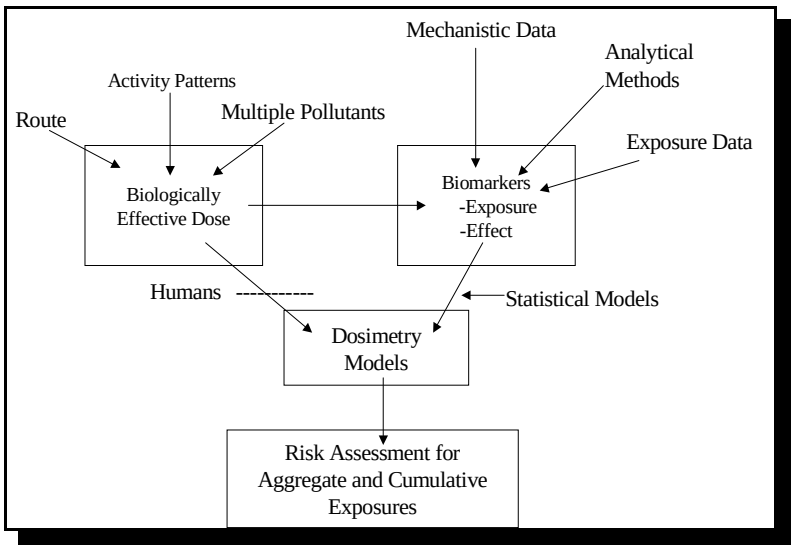
Exposure research on cumulative and aggregate risk will build upon the problem-driven research being conducted under other research strategies (see Appendix A) and focus principally on describing how people come into contact with pollutants. As a result of this emphasis, one important component of this research will be to identify and characterize major factors, including time-activity patterns, that contribute to human variability in aggregate and cumulative exposure, and conduct studies to determine distributions of aggregate and cumulative exposure for the general population and for specific susceptible or targeted subpopulations (see schematic on next page). Exposure research will integrate an understanding of exposure pathways and human contact with pollutants into probabilistic human exposure models that account for both aggregate and cumulative exposures. These exposure models will then be tested against the exposure and

exposure factor data generated through targeted laboratory and field measurement studies, including population and epidemiological studies. The resulting data will be used to improve our understanding of human exposure and refine the exposure models. The ultimate objective of this research will be to assemble and integrate a knowledge of human exposures into models that describe those exposures and to combine the source models, the transport and fate models, and the probabilistic exposure models into an integrated modeling framework, or platform, that can be linked and effectively employed by the risk assessor. The framework is designed to link a variety of source, exposure, exposure-dose, and dose-effect models/modules into a comprehensive source-to-effects modeling framework characterizing and assessing user-specified aggregate and cumulative exposures and risks. The resulting tools, models, and framework will then be disseminated to scientists and risk assessors as they work to solve specific programmatic problems as outlined in ORD's research strategies (see Appendix A).



Exposure to Dose Research. When exposures to an agent occur via multiple routes, they must be converted to a common basis, usually some measure of dose, to evaluate the risk of aggregate and cumulative exposure. Ideally, the common metric would be the biologically effective dose, that is, the dose to the target organ, tissue, cell, or molecule that causes the toxic or adverse health effect (see schematic on next page). The biologically effective dose may be the pollutant itself or one or more metabolites and may be affected by many factors. For example, contemporaneous exposure of a single pollutant by more than one route can result in different proportions of parent compound or metabolites than would be predicted from one route alone. The route of exposure may also modulate the internal dose of systemic toxicants at the target tissue due to alterations in physiological parameters (e.g., breathing rate due to an irritant) or

pharmacokinetic parameters (e.g., induction of enzymes). Human activity patterns may also impact the biologically effective dose. A pesticide, for example, may contact the body through inhalation of dust from contaminated surfaces, the diet, and as a result of hand-to-mouth activity. People may be exposed occupationally as well as incidently away from their place of work. People may also be exposed to low background levels and also, by virtue of special intermittent activities, to bursts of higher exposure. Finally, the biologically effective dose may be affected by exposure to more than one pollutant. Multiple pollutant exposures might change the metabolic transformation of the pollutants in the mixture, resulting in different biologically effective doses than seen after exposure to the pollutants in isolation. Ingestion of otherwise innocuous substances, because of enzyme induction, might also increase the rate of formation of a toxicologically relevant metabolite of a pollutant of environmental concern. Knowledge of the biologically effective dose provides the basis for developing dosimetry models that can be used in assessing risk of aggregate and cumulative exposures.



However, measuring the biologically effective dose in humans is not easily accomplished and is therefore not usually attempted. More often, a surrogate for the biologically effective dose, such as the absorbed dose (the amount of substance crossing an absorption barrier such as the skin, the lining of the lung, or the lining of the gastrointestinal tract) or the level of pollutant in human blood, urine, or other biological tissue, is measured or estimated and used in the aggregate assessment as the common metric. In some notable cases (e.g., concentration of lead in the blood, carboxyhemoglobin), the human biomarker can also be used as a quantitative predictor of effects. An exposure biomarker is an exogenous substance or its metabolite(s) measured in a compartment within an organism, whereas an effects biomarker is a measurable change within an organism that can be recognized as an established or potential health impairment. Exposure biomarkers are

actual evidence of internal dose. However, only a few biomarkers, such as urinary metabolites, are relatively easy to measure in exposure field studies. With proper research, such biomarkers can be used with pharmacokinetic models to estimate, via a "back calculation", the biologically effective dose and even the exposure that occurred. Thus here, the exposure-to-dose continuum is actually used in reverse for "dose-to-exposure" estimations.

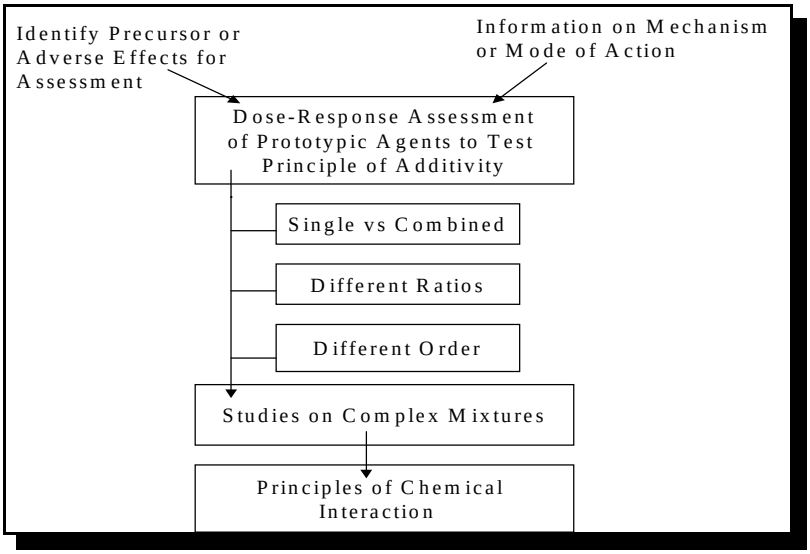
Identification and characterization of biomarkers and development of methods to use them will be a high priority for ORD's research on aggregate and cumulative risk. Development of analytic methods to measure biomarkers and methods for their analysis and interpretation will be necessary for exposure and dose assessment. This will require contributions from ORD's research on effects to provide the scientific basis for the development of sensitive and specific biomarkers based on mechanistic studies. Combined with proper modeling techniques and some knowledge of possible exposure patterns and measurements, biomarker data can be used to estimate dose and exposure. Research in this area will also focus on the development and/or implementation of advanced statistical methods to help formulate and use dosimetry models for estimating exposure from biomarkers. This is especially important as more and more biomarker measurements are taken and their results are made available. For example, CDC is publishing on the internet the results of such measurements taken in the population. Those data, often representing "snap-shots in time" will have to be interpreted using a variety of modeling and statistical tools to determine the meaning of these data with respect to exposure and dose.

Initially, ORD's dose research will focus on the development of a suite of route-specific models for use in dose-response assessment of cumulative and aggregate exposures. This will build upon the dosimetry-based approach in the current risk assessment guidelines, extend it to oral and dermal exposures, and use it to evaluate aggregate exposures. As the program progresses, dose models will be expanded to describe and predict chemical disposition within the body resulting from aggregate and cumulative exposures. ORD's dosimetry models will enable users to estimate biologically relevant doses resulting from exposure to multiple pollutants and multiple pathways of exposure. The most immediate phases of this research will concentrate on aggregate exposures. In addressing cumulative risk, models will be first developed for those cases involving

exposure to multiple compounds with common modes of action. The next phase will begin to address those cases where compounds may act with different modes of actions.

ORD realizes that there must be significant integration between research on exposures, dose and effects to study the problem of aggregate and cumulative risk adequately. ORD has already implemented plans to facilitate a multidisciplinary approach to this problem. For example, scientists from NERL, NHEERL and NCEA, as well as scientists from the Office of Pesticide Programs (OPP), are working on a collaborative research project to develop methods and models for assessing the exposure, dose, and aggregate and cumulative risk of pyrethroid mixtures. In addition, NERL and NHEERL sponsored a Exposure to Dose Modeling Workshop in July 2001 to begin linking quantitative modeling in a Human Health Risk Assessment context. This scientist-to-scientist meeting examined a number of issues related to source, exposure pathways, doses in toxicology and epidemiological studies, pharmacokinetic modeling of mode of action, effects, and dose-response modeling. Scientific presentations at the meeting were followed by a discussion of research directions and options for linking models. Significant opportunities for collaboration and model-sharing between principal investigators in both laboratories were identified. Plans are being made to integrate to a greater extent the modeling efforts of the two laboratories. Interactions between the exposure, dose, and effects research programs and the risk assessment methods are also being developed.

Effects Research. The FQPA indicates that the EPA must consider the cumulative effects of pesticides and other chemicals having a common mode or mechanism of toxicity. Understanding cumulative risk requires knowledge about mechanisms or modes of action and an understanding of how chemicals will interact in mixtures. The principal effects issue for cumulative risk concerns the possibility that chemicals in mixtures may interact in a nonadditive manner. There is evidence that the assumption of dose additivity may not hold for all mixtures of pollutants. For example, research has indicated that antagonism can occur at high concentrations of some mixtures of pollutants, whereas synergistic interactions have been noted at the low end of the dose-response curve for other mixtures. Understanding the conditions under which nonadditive interactions will occur between pollutants is needed to support risk assessment approaches for cumulative exposures.



ORD's effects research program on mixtures will test various assumptions concerning the behavior of pollutants in defined mixtures containing major or key known constituents at concentration ratios resembling real world mixtures. It is crucial in these studies to understand dose-response behavior and the pharmacokinetic characteristics of each pollutant to develop quantitative models. Much of this information can be derived from projected work on the development of methods and mechanistically based dose-response models. It is likely that a systematic approach to the study of mixtures will require the development of new investigative tools such as genomics and proteomics so that effects of multiple pollutant interactions can be studied in rapid fashion.

The overall approach of ORD's effects research on chemical mixtures will be to identify key biological processes (see schematic above) that could be used in testing for various health endpoints and determining effects of pollutants based on their mechanism or mode of action and environmental relevance. Initial studies will focus on dose-response curves for pollutants in isolation, and then pollutants will be tested for evidence of antagonism, potentiation, or synergism with other pollutants in mixture. One key question is where on the dose-response curve interactions occur, and if interactions vary with the ratio of the pollutants in the mixture. Another important question is the influence of the order of presentation of pollutants in the mixture. Studies on interactions between pollutants in mixtures will be used to develop principles for the assessment of real-world mixtures.

Risk Assessment Methods. Human populations are most frequently exposed to multiple environmental pollutants and other stressors (e.g., particulate matter, pesticides, microbes, climatic stressors). Exposure to multiple stressors could change health risks through combining

effects arising from similar modes of action, or through interactions between nonchemical stressors that increase or decrease the potency of environmental agents. Research will be designed and conducted to evaluate population-based approaches to assess effects of total exposures in the environment and the interaction of chemicals with nonchemical stressors. Because this is an emerging area, case studies will be conducted and a conceptual framework will be developed incorporating results from ORD aggregate/cumulative research and addressing issues of aggregate and cumulative exposure, mechanisms of action, and PBPK and dose-response modeling. The objective of this research is to develop guidance and EPA guidelines for population-based cumulative risk that will incorporate cumulative and aggregate exposure to multiple stressors.

2.3 Research on Susceptible and Highly-Exposed Subpopulations

Observed variability in human responses to environmental agents reflects differences in biological susceptibility and exposure. Variation in biological susceptibility depends on intrinsic factors (e.g., life stage, gender, genetic factors, physiological state) and acquired factors (e.g., preexisting disease, activity levels, nutrition, stress, licit and illicit drug use, cigarette smoking, and alcohol use). Variation in exposure and dose can be influenced by many of the same factors. In addition, factors such as occupation, location of residence, and activity patterns that place individuals in contact with environmental agents cause variation in exposure. Information is needed on how various susceptibility and exposure factors alter responses to chemical exposures. ORD research on susceptible and highly-exposed subpopulations will focus on three factors: life stage, genetic factors, and preexisting disease.

Other ORD research strategies which address susceptible and highly-exposed subpopulations are the *Strategy for Research on Environmental Risks to Children* (U. S. EPA, 2000a) and the draft *Asthma Research Strategy* (U.S. EPA, 2001a). The influence of life stage on responsiveness to endocrine disruptors is described in the *Research Plan for Endocrine Disruptors* (U.S. EPA, 1998).

2.3.1 Scientific Uncertainties

Life Stage. There are specific periods or windows of vulnerability during development, particularly during early gestation but also throughout pregnancy and early childhood through adolescence, when toxicants might permanently alter the morphology and/or function of a system (Rodier 1980; Bellinger et al. 1987). Children may also be more vulnerable to specific environmental pollutants because of differences in absorption, metabolism, and excretion (NRC, 1993). In addition, children's exposures to environmental pollutants are often different from those of adults because of different diets and different activities (e.g., playing on floors and in soil and mouthing of their hands, toys, and other objects) that can bring them into greater contact with environmental pollutants (Bearer, 1995). Because children consume proportionately more food and fluids, have a greater skin surface area relative to their body weight, and breathe more air per unit body weight than adults, they may receive greater exposure to environmental substances (NRC, 1993). These health threats to children are often difficult to recognize and assess because of limited understanding of when and why children's exposures and responses are different from those of adults.

The impact of aging on response to environmental exposures is another area of uncertainty based on life stage. The elderly may respond differently from younger adults to environmental exposures. There may be an increased risk of cancer and degenerative diseases as a function of age. The prominence of these concerns is rapidly elevating with the largest birth cohort in the US, namely, the "baby boomers", now becoming senior citizens. Many of these individuals are living longer and the impact of previous exposures may be markedly magnified with aging. Research is needed to examine the impact of the aging process on responses to environmental pollutants and to develop predictive models that can be incorporated into the risk assessment process.

Genetic factors. There are a number of genetic factors that could predispose human subpopulations to adverse effects from exposure to pollutants, including genetic polymorphisms for metabolizing enzymes, differing rates of DNA repair, and different rates of compensation following toxic insult. The main scientific question for this research is whether such genetic differences significantly influence risk at realistic, low dose exposures. Information on gene-pollutant interactions as a result of long-term exposure to environmentally relevant concentrations of pollutants is needed.

Health status. Preexisting diseases may influence the response to environmental toxicants by altering xenobiotic metabolism or otherwise altering the host's response in a synergistic, additive, or antagonistic manner. ORD research has shown, for example, that mice challenged with influenza have increased mortality from exposure to several environmental agents including dioxin, ozone, and ultraviolet radiation. Research is need to develop animal models of diseases having a high incidence in the human population and determine the effects of the disease on the dose-response curves for high priority environmental agents (e.g., air pollutants, pesticides).

2.3.2 Research Objectives

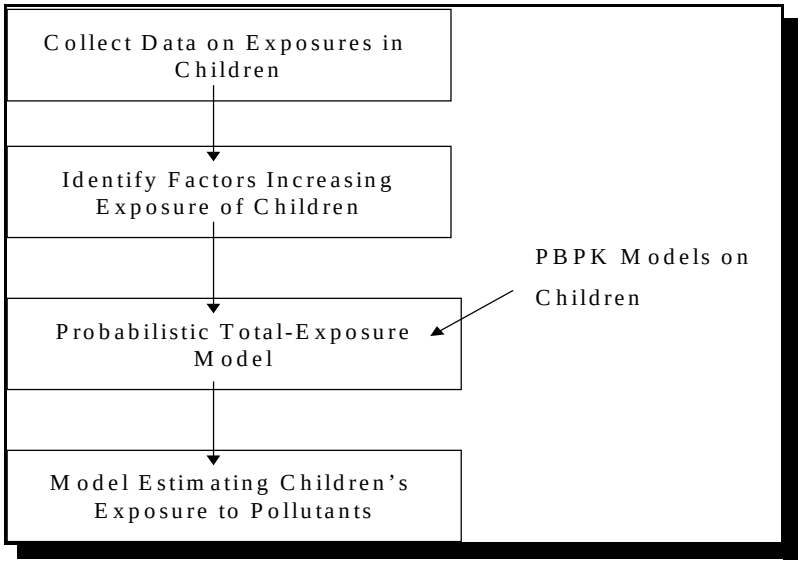
The *Human Health Research Strategy* provides a broad framework for ORD research in human variability. Issues specifically related to children's risk are also covered in more detail in the *Strategy for Research on Environmental Risks to Children* (U.S. EPA, 2000a), the *Strategic Plan for Endocrine Disruptors* (U.S. EPA, 1998) and the *Asthma Research Strategy* (U.S. EPA, 2001a). The following research objectives provide the framework for an integrated research program on variability in the human population:

- -Identify the key factors that contribute to variability in human exposure, including the distribution of human exposures and behavior associated with exposure to pollutants;
- -Improve the accuracy of dose estimation in the general population;
- -Identify the biological basis underlying differential responsiveness of sensitive subpopulations of humans to pollutant exposure;
- -Determine how exposure, dose and effect information can be incorporated into risk assessment methods to account for interindividual variability.

2.3.3 Research Approach

Exposure Research. Although an average person may not be exposed to an environmental agent at a level that would cause a health concern, a small percentage of the population may have significantly higher exposures because proximity to sources or activities increase likelihood of

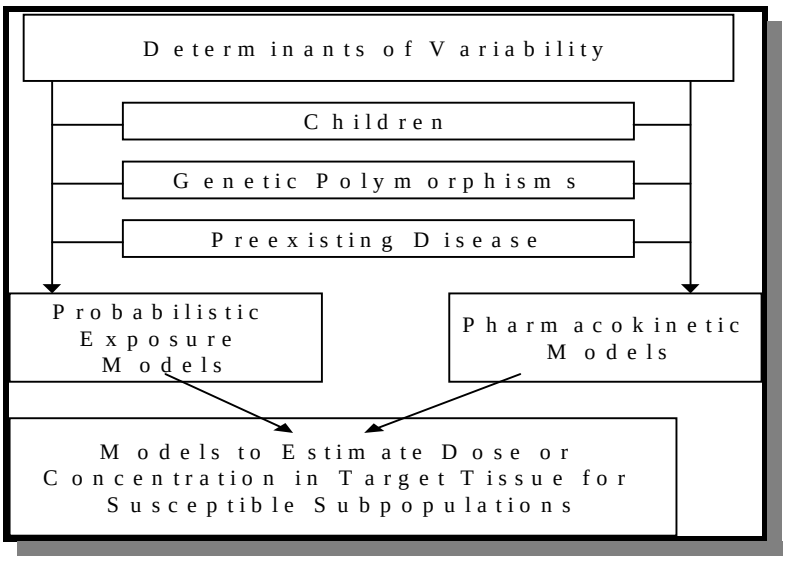
exposure. Therefore, exposure assessments should include distributions of exposures to allow identification and assessment of groups of people at risk from high-end exposures. Exposure assessments should also account for the exposures of people who may be especially susceptible.



ORD's exposure research will focus primarily on children. The overall objective is to develop a broadly applicable probabilistic total-exposure model capable of linking to a PBPK model to estimate children's exposure (see schematic above). ORD will collect data on children's exposures and factors that influence exposure. These data will provide input to the development of a probabilistic model. Status and trends in children's exposure to environmental agents will also be characterized. Highly exposed subpopulations of children will be identified and important sources and pathways of children's exposures will be delineated. Residential exposure factors for children will be characterized by age and sex for the national population, regional populations, highly exposed groups, and susceptible groups. Factors that will be characterized include activity patterns (time spent in a given activity and frequency of occurrence), soil and dust ingestion rates, factors reflecting transfer of environmental agents from objects and surfaces children commonly touch, and factors related to ingestion of pollutant residues on surfaces.

Dose Research. Dose research in the area of susceptible subpopulations will focus on developing probabilistic exposure and pharmacokinetic models which estimate doses in susceptible subpopulations, including children and those with genetic polymorphisms or preexisting disease (see schematic on next page). This research will provide crucial information on the likelihood that a pollutant or its metabolites will be present at the target site, the concentrations in target tissues, and whether and how the dose varies between members of the general population and susceptible individuals. Measuring and modeling the impact of

susceptibility factors on dose will help ORD design and conduct studies of the biological mechanisms on the cellular and molecular levels that lead to adverse effects. This will lead to a better understanding of the biological bases for differential sensitivity of susceptible subpopulations.

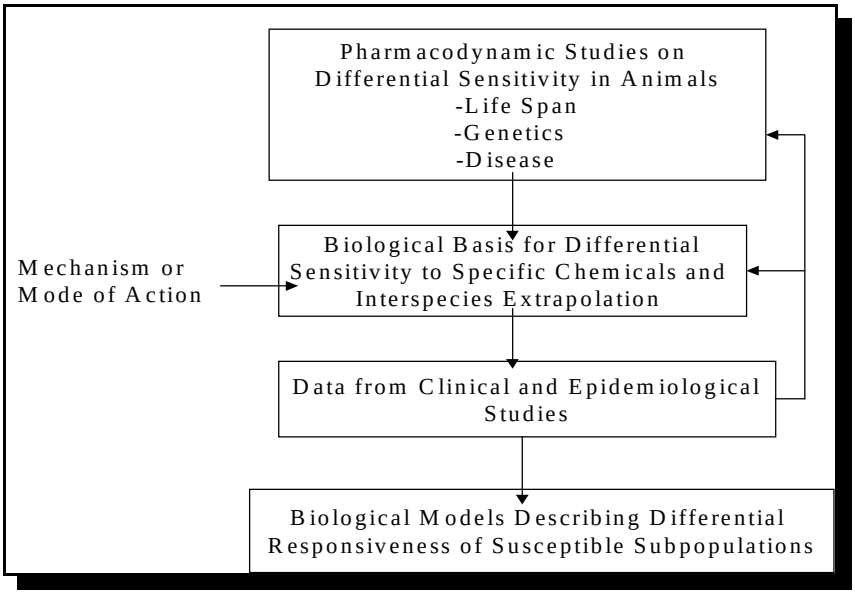


For the near term, ORD will continue its focus on children. Broadly applicable PBPK models and methods will be produced that allow better quantitative characterizations of dose to target tissue in developing organisms to replace default assumptions in children's risk assessments. Over the next 3 to 4 years, research on the influence of genetic polymorphisms and disease status on pharmacokinetic parameters will increase.

The development and linkage of probabilistic exposure and pharmacokinetic models (e.g., PBPK models) will provide valuable tools for analyzing and utilizing data describing variations in subpopulations in risk assessment. A key factor will be to establish methods and approaches that can be applied to both animals and humans to aid in extrapolating from dose-response data collected in animals to humans.

Effects Research. The main hypothesis of the effects research on susceptible subpopulations is that differences among individuals (interindividual) as well as the variability in an individual's responses over time (intraindividual) are due to biological variability. ORD's effects research on susceptible subpopulations will focus on developing biological models that describe differential sensitivity of various subpopulations for risk assessment, especially the influence of life stage, genetic factors and preexisting disease on toxicological outcome or adverse health effect (see schematic on next page).

Life Stage. There is now evidence that differential sensitivity of very young (early postnatal, children) and elderly individuals to certain pollutants may be related to pharmacokinetic factors. In conjunction with ORD's dose research program, the effects research program will develop longitudinal pharmacokinetic information for prototypic environmental agents from the prenatal and early postnatal period to senescence in laboratory animals to determine how specific xenobiotic metabolizing enzymes change as a function of lifestage. Research will also determine how biological changes specific to some life stages (e.g., proliferative phase during development) can increase risk of certain pollutants. Identification of such pharmacodynamic factors is crucial for the protection of susceptible subpopulations at different stages of development. As in the case of research on exposure, a major emphasis will be on children. An objective of this research will be to link developmental effects at the tissue, organ, and system levels with the underlying effects at the cellular and molecular levels and to develop the first-generation of biologically based predictive models. Information from dose-response, pharmacokinetic, and mode-of-action studies in animals will be incorporated into models that more accurately predict children's risks.



Effects research currently focuses on the effects of pollutants on early stages of development. As more is known about the effects of pollutants on infants and children, research efforts will begin to examine the influence of early exposure to pollutants on health status later in life. Of particular concern is the increased risk of cancer and neurodegenerative diseases as a function of age based on earlier exposures. Multidisciplinary approaches will be developed in animal models to examine the impact of environmental pollutants on the aging process and to develop predictive models that can be incorporated into the risk assessment process. Epidemiology studies will be crucial to understanding whether certain groups are more

susceptible to environmental contaminants than others and such studies will be conducted by all Laboratories and Centers in ORD. Hypothesis-based human epidemiologic and clinical studies will be necessary to identify and confirm that adverse effects occur in humans, identify risk factors, develop dose-response relationships in humans, and improve extrapolations from animal data to humans. Human studies will be conducted as needed for high-priority environmental agents and to assist in model development and validation.

In the Children's Health Act of 2000, Congress directed the National Institute of Child Health and Human Development to establish a consortium of Federal agencies, including EPA and the CDC, to design and implement a National Children's Study. The Study will follow a cohort of children from as early in pregnancy as possible to adulthood to evaluate the effects of chronic and intermittent exposure on child health and human development. The goal is to enroll at least 100,000 children in the study. Exposure information will be collected for preconception exposures, at several times during pregnancy, and at several ages after birth, and outcome data will be collected during pregnancy, infancy, childhood, and beyond, perhaps focusing on developmental milestones of potential susceptibility in each of several age ranges. Biological specimens from the parents and children will be collected. Children will be followed at least through their primary school years, and preferably into adulthood. ORD is participating in the planning and design of the study and developing and testing methods for data collection. Through this study, ORD will identify environmental agents and other factors contributing to adverse effects in children and characterize the status and trends in children's exposure and health. ORD plans to conduct much of its research on childhood asthma through this study.

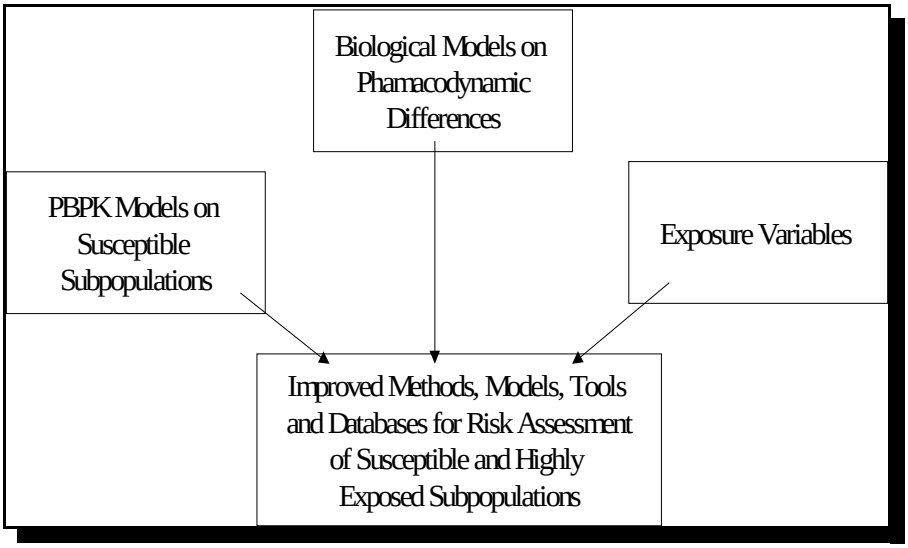
Genetic Differences. ORD's effects research on genetic influences will address the hypothesis that individuals harboring genetic polymorphisms in metabolic genes may have increased vulnerability to health effects following exposure to some pollutants. ORD research has shown, for example, that people who are phenotypic for rapid acetylation have higher levels of urinary mutagens following exposure to heterocyclic amines in food. The main scientific question for this research is whether such genetic differences significantly influence risk. This research will focus on the influence of genetic factors on long-term exposure to low levels of pollutants. The

role of other genetic factors in susceptibility, such as differing rates of DNA repair and compensatory responses to toxic insult, will also be investigated.

Disease. Preexisting diseases may influence the response to environmental toxicants by altering xenobiotic metabolism or otherwise altering the host's response in a synergistic, additive, or antagonistic manner. Research will focus on the development of animal models of diseases having a high occurrence in the human population (e.g., asthma, bronchitis, hypertension) and determine the effects of the disease on the dose-response curves of high priority environmental agents (e.g., air pollutants, pesticides). Mechanistic research will establish animal models that employ specific host traits that are characteristic of the disease and represent "risk factors" for the increased sensitivity to chemicals. Once effects have been established using these animal models, studies will be conducted to extrapolate from rodent data to human effects and across levels of biologic organization. Epidemiological studies will also be used to identify possible associations between exposure to a specific pollutant and manifestation of a disease. Such associations will then be tested in *in vitro* or *in vivo* animal models. Data derived from these studies can be used to assess the possible increased risk to pollutant exposure in individuals with preexisting disease. Research on health status will continue to focus on asthma and other respiratory diseases and air pollution; studies on other diseases and pollutant classes will be conducted as time and resources allow.

Risk Assessment Methods Research. The results of ORD's research in exposure, dose, and effects, along with research supported by other government agencies and nongovernmental sponsors will be used to develop improved methods, models, tools and databases for risk assessments of susceptible and highly exposed subpopulations (see schematic on next page). ORD will use pharmacodynamic data and PBPK models from research on effect and dose to develop better dose-response methodologies to account for susceptibilities of various life stages and to evaluate the adequacy of the current default uncertainty factor of 10 in accounting for human variability for noncancer health effects. ORD risk assessment methods research will also analyze data on exposure factors, human activity patterns and environmental concentrations, including those generated by the exposure research program on pesticides and air pollutants, to quantify the important factors used in exposure assessment and to evaluate representativeness of the data based

on factors such as life stage, genetics, and pre-existing disease. Databases on physiological and pharmacokinetic factors for various life stages will be developed to aid in development and implementation of PBPK models. Dose-response methodologies for specific life stages, accounting for differences between children and adults, will be developed. Distributions of exposure factors measured in ORD studies will be incorporated into the Exposure Factors Handbook (U.S. EPA, 2000b, 1997b). Finally, ORD will develop guidance for performing risk assessments for children, the elderly, and those with preexisting diseases, and guidance for taking into account genetic variation in risk assessment.



3. RESEARCH TO ENABLE EVALUATION OF PUBLIC HEALTH OUTCOMES FROM RISK MANAGEMENT ACTIONS

The United States General Accounting Office's (GAO's) report on exposure to toxic pollutants estimates that total environmental compliance costs will be about $148 billion in 2000 (GAO, 2001). Understanding the efficacy of such large expenditures and being able to evaluate public health outcomes that are expected has tremendous value for EPA decision-makers, as well as those in other organizations affected by EPA decisions. This is particularly true when EPA is faced with several possible risk management actions that might be employed as part of the decision-making process. With the advent of the Government Performance and Results Act (GPRA) and calls for the EPA to stress and demonstrate outcome-oriented goals and measures of success, research is needed to enable evaluation of actual public health outcomes from risk management actions. Estimating public health benefits of EPA regulatory decisions and rule making, or in a more general sense evaluating public health outcomes from risk management actions, will be a challenging undertaking. It will involve a number of disciplines grounded in both the physical and social sciences, and increasingly must take into account the economic and behavioral aspects of human decision-making.

Evaluating public health outcomes from risk management actions is clearly linked to assessing human health risks. EPA risk assessors and risk managers must consider the uncertainties associated with the risk assessment process. Increasingly, they must objectively take into account the uncertainties associated with various risk management actions and their intended outcomes. Coupled with these uncertainties is the fact that the EPA very often estimates the future benefits of public health outcomes in a politically-charged environment. Depending on the desired human health protection endpoint, final decisions often rest with national and State policy makers and decision officials. These officials take scientific findings into account along with a number of other considerations that assist them in making more informed public policy decisions.

Generally, EPA has not prepared retrospective evaluations examining whether the intended benefits in protecting public health were realized once an EPA decision has been in place for a

period of time. One exception to this was the decision to ban lead in gasoline and other products, the subsequent tracking of blood-lead levels in children as a result of the ban, and then studies confirming the linkage between elevated blood level levels and reduced cognitive development in children as a result of the ban. The confounding influences of various factors (e.g., age of exposure, duration of exposure, exposure to other pollutants alone or in complex mixtures) offer challenges at every turn in evaluating public health outcomes. As the EPA develops and implements a research program advancing the evaluation of public health outcomes, either prospective or retrospective, participants and observers must recognize that the program will take years, perhaps decades to develop and fully implement. It will involve a number of organizations both within and outside of the EPA working in partnership to collect and analyze data and then use that data in methodologies and tools to objectively determine the effectiveness of risk management decisions on public health outcomes.

> The Presidential Commission on Risk Assessment and Risk Management points out the need for progress in several scientific areas, "if we are to improve our ability to implement and measure the effectiveness of public health interventions. Specifically, we need to: (1) Link studies of exposure and studies of adverse health or ecological outcomes; (2) Determine regional differences in disease prevalence and disease incidence trends and risk factors; (3) Develop good baseline and surveillance information about incidence rates of diseases specifically linked to environmental causes; and (4) Identify the most important environmental causes of diseases" (page 47, vol. 1).

The Presidential Commission on Risk Assessment and Risk Management (1997) has supported the need for EPA to measure the effectiveness of public health interventions (see text box). The National Research Council (1997) also noted a lack of consensus concerning appropriate indicators of health status that could be used to measure the performance of environmental health programs. This has led the Council of State and Territorial Epidemiologists, the CDC, the Agency for Toxic Substances and Disease Registry, and the EPA to begin the development of a set of public health indicators to track adverse health events related to the environment. The Pew Environmental Health Commission (Pew, 2000) has also recommended a nationwide tracking of priority chronic diseases, such as asthma and respiratory diseases, and exposures to environmental pollutants such as PCBs, metals, and pesticides.

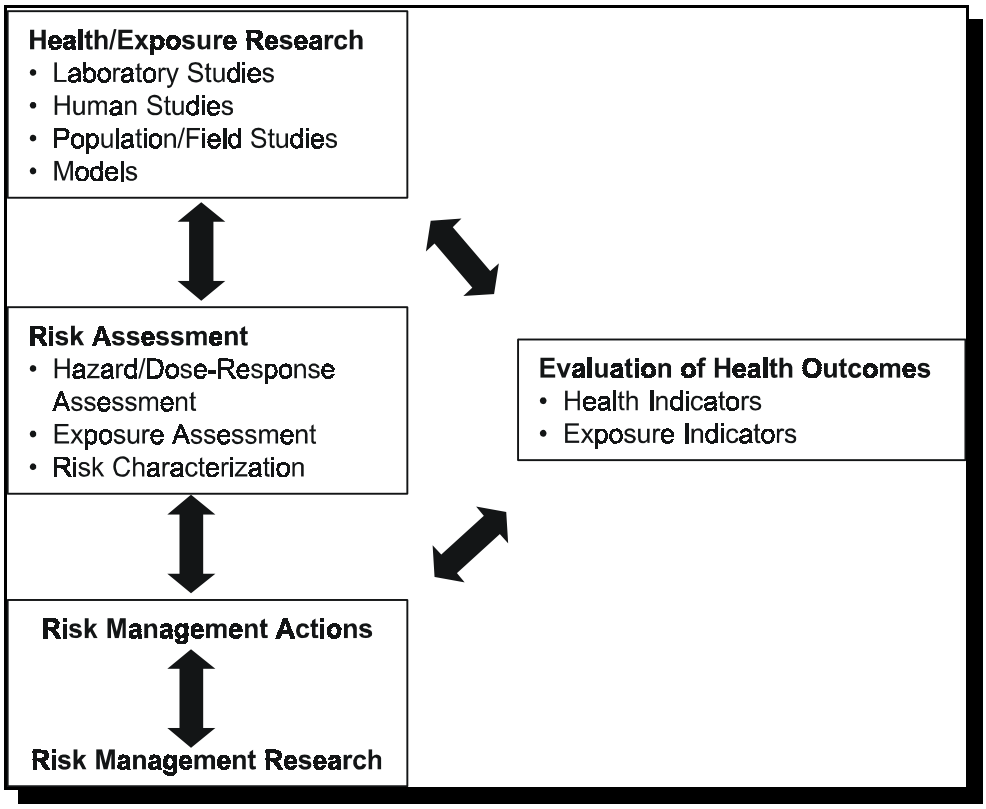


Figure 3-1. Role of analysis of health outcomes in the risk management decision process.

Chapter 2 of the *Human Health Research Strategy* set forth priorities for improving the science of human health risk assessment. These improvements will result in more effective and longer lasting risk management actions and will contribute to public health outcomes that can be achieved. Chapter 3 describes research enabling more informative and reliable evaluations of public health outcomes (e.g., improved estimates of actual reductions in risks to public health via exposure and effects data) from risk management actions. Taken together, these two chapters will mutually inform each other as the Human Health Research Strategy is implemented in the years to come.

3.1 SCOPE AND DEFINITIONS

As discussed in Chapter 1, there are great similarities in information needs for risk assessment and risk management. This is because understanding the efficacy of an EPA decision

requires a comparative analysis of risks before and after implementation of risk management actions (see Figure 3-1). At the same time, various risk management actions must be applied within the framework of maximum achievable risk reduction that is efficient, cost-effective and long-lasting. Important issues need to be addressed that require research targeted at the most robust possible evaluation of public health outcomes from risk management actions.

Definitions of Key Terms (Haddix et al., 1998)

Effectiveness-The improvement in health outcome that a prevention strategy can produce in typical community-based settings (p.146).

Efficacy-The improvement in health outcome that a prevention strategy can produce in expert hands under ideal circumstances (p.146).

Outcome Measure- The final health consequence (e.g., cases prevented) on an intervention (p.149)

This chapter stresses the identification of existing, and the creation of new information that can be used in evaluating public health outcomes from risk management decisions. Reflecting the close relationship between risk assessment and risk management, this public health outcomes research program is included in the *Human Health Research Strategy* for two reasons: (1) the need to link more closely risk assessment and risk management so as to improve human health risk assessments, and (2) the need to improve the scientific basis for evaluating public health outcomes from risk management actions.

It is essential for the research described in this chapter to be based upon a common set of definitions. Haddix and others, in their *Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation* (1998), offer a set of useful definitions adopted for this research strategy (see text box above). The remainder of this chapter discusses the scientific uncertainties underlying the evaluation of public health outcomes from risk management actions and describes the research approach to meet the objectives of ORD's public health outcomes research program.

3.2 SCIENTIFIC UNCERTAINTIES

The basic philosophy behind the EPA's public health policies is that regulatory or other risk management actions are taken with the intent of preventing or reducing releases of pollutants of concern. This philosophy assumes that exposure prevention or reduction will lead to measurable reductions in specific human health effects. However, actual reductions in health effects will depend on the proportional relationships between the pollutant releases and health risks from a given source as well as whether the health risks are dependent on other sources not being considered. The degree of certainty and directness of these links between source, exposure, and effect influence the validity of this assumption. Behavior of individuals in reducing risk is also an important variable.

Unfortunately, in most cases, this linkage has a very poor quantitative scientific foundation, and health-protective default assumptions are generally used in cases of uncertainty or lack of information. If this linkage were better forged scientifically, it could predict risk management action effectiveness more accurately. Even so, actual impacts will need to be measured to evaluate whether the predictions (or the prediction approach) are correct. The optimal approach is to compare a health risk assessment before and after the risk management action has been employed. This is, however, a very complex and challenging undertaking because a systematic framework for doing so does not exist. Prospective assessments of risk often use approaches with varying degrees of sensitivity and reliability. Furthermore, even if prospective assessments were reliable, they may not be suitable for a retrospective analysis. For example, an epidemiologic study with sufficient sensitivity for prospective risk assessment may not have the statistical power to detect the expected risk reductions. In addition, if the expected public health outcome is the lessening of a chronic effect (e.g., cancer), it may take many years to be detected with current risk assessment approaches that use cancer incidence as the endpoint. Finally, some risk management actions create multiple and perhaps disparate benefits and possibly unintended consequences. This causes great difficulty in the analysis of management actions because the unintended impact has to be identified and evaluated.

Long-Term Goal- Provide the scientific understanding and tools to assist the EPA and others in evaluating the effectiveness of public health outcomes resulting from risk management actions.

Key Scientific Questions- How can the most effective tools, systems, methods and models be identified, discovered, or developed and then integrated into a decision-making framework, to assist Federal, State and local decision-makers in evaluating changes in public health as a result of risk management actions? What is the ability of this framework to quantify such changes accurately?

3.3 SCIENTIFIC OBJECTIVES

Two research objectives were developed based on 3 research questions described below. The research questions were developed in accordance with the Long-Term Goal and Key Scientific Questions described above. The research questions serve as the foundation upon which to develop a coherent framework for an integrated research program and include the following:

-What kinds of policies or regulations should be evaluated to determine the efficacy of risk management actions?

-What approaches are available to address the effectiveness of risk management actions on public health?

-What improvements are needed to the approaches, and will these improvements result in a more useful framework for evaluating public health outcomes?

Admittedly, achieving the Long Term Goal and answering the Key Scientific and associated research questions will take considerable time and effort on the part of both ORD and others. All components of ORD, its three national Laboratories and two national Centers, have agreed to work on this public health outcomes research program together; however, neither ORD nor EPA proposes to undertake this research alone. The research program described here will be a daunting undertaking and one that must rely on the contributions of a number of different organizations. It will require feedback loops, engagement, and partnering with other organizations both within and outside the EPA if it is to succeed.

ORD's research will provide the scientific understanding and tools to assist the EPA and others in evaluating public health outcomes resulting from risk management actions. The public health outcomes research program is designed to address the long-term goals and key scientific questions in a stepwise fashion from reductions in releases through reductions in exposure to improvements in public health. It is not designed to be an expansion of the EPA's epidemiological research program, but will rely on collaborations with, and data and information from, other Federal, State, and public health organizations. Ultimately, the tools, systems, methods, and models and the framework within which they operate should measure or reliably estimate changes in human health risks with a known level of precision and accuracy. This precision and accuracy should be sufficient to allow the EPA to determine how its regulatory decisions and risk management actions contributed to those changes. Two specific objectives of ORD's research program emerge:

-Establish linkages between sources, environmental concentrations, exposure, effects, and effectiveness such that a change in a public health outcome consequent to a risk management action can be determined by measuring or modeling any one of these linked steps; and

-Improve tools, systems, methods, and models by which others can measure or model changes in public health outcomes following risk management actions.

It should be noted that a substantial part of the research on the complex relationship between sources and environmental quality (i.e., fate, transport, and transformation) is contained within problem-driven research programs (e.g., particulate matter, air toxics, hazardous waste) (see Appendix A). Research on effectiveness of public health outcomes will provide the linkages to these other related research programs.

General precedents indicate the feasibility and utility of meeting these two objectives. For example, effectiveness evaluations have been conducted for diverse risk management actions (e.g., for pharmacologic therapy, vaccine efficacy, and smoking cessation). These evaluations are becoming more commonplace, and several groups have attempted to provide guidance for the conduct of such studies (Gold, 1995; Graham, 1998; Haddix et al., 1998).

3.4 RESEARCH APPROACH

In developing research program priorities and a deeper understanding of the relationships between risk management actions and public health outcomes, it will be necessary to select cases to study based on the suite of risk management actions that might be employed by the EPA. A decision on the appropriate number and scope of the case studies will be made after further deliberations in workshops and other fora both internal and external to EPA. Particular emphasis will be placed on policies or regulations attendant to risk management that the EPA has developed, is developing, or may be faced to develop within the next 10 years. This type of approach will require close collaboration with EPA's Program and Regional Offices. Study sites and the selection of appropriate research approaches will vary depending upon the environmental exposures and effects of interest.

To ensure full coverage of the possible risk management alternatives, classes of risk management actions will be identified as the first step in the case study process. These classes of action include, but are not limited to, those that: (1) reduce exposure to pollutants currently in the environment; (2) dispose of or redistribute substances currently in the environment; and (3) license (or allow) new substances into the environment or allow levels of substances already in the environment to be increased. Coupled with these classes of risk management actions will be an identification of their implications for evaluating public health outcomes.

Efforts to ascertain the effectiveness of risk management actions will depend on the selection of pertinent research approaches and appropriate indices of public health exposure and effects outcomes. An evaluation of the public health outcome of a risk management decision should answer two questions:

-Did the risk management action actually prevent, reduce, eliminate, or modify exposure to the pollutants of concern?

-Did this prevention, reduction, elimination, or modification result in disease prevention and improved public health?

Four approaches might be used to assess public health outcomes: (a) epidemiologic studies, (b) population exposure studies, (c) field sampling of environmental media, and (d) measuring changes in source emissions. Coupled with this will be the need to investigate and evaluate the performance of models used to estimate outcomes when measurement data may be inaccessible or too costly to collect except as a representative sample. These approaches are ordered in terms of ability to determine human exposures and link them with public health outcomes; however, this ordering does not mean that an approach listed before another approach is necessarily more feasible. Using these approaches effectively in evaluating public health outcomes from risk management actions will require linking them in the development of a framework or model. Each of these areas can be improved, in some cases as a result of the risk assessment research program discussed in Chapter 2. However, there are some special needs for evaluating regulatory efficacy for public health protection. Thus, a careful analysis and prioritization of the approaches *vis-a-vis* the risk management action classes described above are essential.

Although the above approaches are listed discretely, perhaps the greatest challenge of the public health outcomes research program will be to provide linkages among them. Ultimately, this will vastly increase the feasibility and accuracy of both prospective and retrospective risk assessments. Given the immense number of scenarios to be evaluated, models of this process are needed. Such models are under development as part of the core research program described in Chapter 2, but additional models are likely to be required that incorporate the special needs of an retrospective assessment and more thoroughly link the approaches under consideration.

To assess the strengths and weaknesses of evaluating public health outcomes from risk management actions, a logical first step will be to use existing approaches and evaluate available databases that compile pollutant release information and environmental concentrations, health endpoints, or both. Appendix E lists some databases and other sources that contain information that could be used to correlate health endpoints with concentrations of pollutants. Such an exercise will likely identify priorities for future research. Better ways to measure changes in effects (or in indicators of effects, exposure, indicators of exposure, environmental concentrations, or source strength) are needed, together with programs to measure the effects before and after implementation of the EPA's decisions.

Risk management tools are needed that express the EPA's understanding of the cost-effectiveness and long-lasting nature of risk management actions, and convey that understanding to other regulatory offices, the regulated community, and the public. Finally, a framework to link models all the way from source to human health effects provides more confidence in exposure-dose-response relationships through a thorough understanding of the critical processes within, and linkages between, each component of the human exposure-dose-response sequence.

3.5 RESEARCH IMPLEMENTATION

The ultimate goal of ORD's public health outcomes research program is to provide a set of fully developed frameworks and a suite of technical tools, systems, methods, and models that assist the EPA and others in evaluating public health outcomes from risk management actions. The research program will require the full participation and active engagement of stakeholders at all levels, both internal and external to the EPA. It must leverage the research program with other public- and private-sector organizations involved in similar or compatible efforts since that is the only way it will succeed. The Long Term Goal to provide the scientific understanding and tools to assist the EPA and others in evaluating the effectiveness of public health outcomes resulting from risk management actions is extremely ambitious and research in this area will proceed in a step-wise and incremental fashion as described below.

Development phase. This phase will provide a comprehensive state-of-the-science evaluation of currently available domestic and international tools, systems, and methods, along with frameworks that are being, or could be, used in evaluating public health outcomes from a variety of risk management actions. It will of necessity partner with EPA Program and Regional Offices and will seek to engage organizations outside the EPA that are positioned to engage in a public health outcomes research program.

Investigation phase. This phase will implement a detailed multiyear research plan for improving various tools, systems, and methods (existing and new) to evaluate public health outcomes from risk management actions. A preliminary compendium of tools, systems, and methods, along with selected framework(s), will be developed. Pilot investigations and case studies

on evaluations of health and exposure information will also be conducted, leading to further refinements of the frameworks.

Delivery phase. This phase will provide a set of fully developed frameworks and a suite of technical tools, systems, and methods for use by various stakeholders. This compendium will be closely coupled with illustrations and training on its use, along with case studies targeting decision-makers at multiple levels.

As discussed above, a near-term objective of this research program is to develop a framework and a multiyear implementation plan for undertaking research on evaluating public health outcomes from risk management actions. Recommended next steps include the following:

-Conduct workshops, in consultation with Federal, regional, State, and local decision-makers and other interested parties, to develop a comprehensive state-of the science evaluation and to identify the elements of a possible framework (or frameworks) for evaluating public health outcomes from risk management actions.

-Describe a set of specific cases/situations that are potential targets for case studies (including rationale) for evaluating public health outcomes from risk management actions.

-Through ORD's STAR program, issue a request for application on the development of statistical techniques using environmental and human health data in evaluating public health outcomes, and conduct case studies to test these techniques.

-Assess state-of-the-science approaches for evaluating how human health is impacted by risk management actions.

-Identify the policies and regulations that would most likely benefit from the use of a framework and set of tools that evaluate public health outcomes from risk management actions.

-Understand how various decision-makers at the national, regional, State, and local levels currently use, or might use in the future, various frameworks and tools for evaluating public health outcomes from risk management actions.

-Identify a set of environmental health indicators that can be used to evaluate effectiveness of risk management actions on public health.

Components of the research program must address such factors as likelihood for case studies to be informative and useful, and the composition of research designs to achieve the desired long-term goals of the research program.

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APPENDIX A

ORD Research Plans and Strategies

Final Research Plan for Microbial Pathogens and Disinfection By-Products in Drinking Water (U.S. EPA, 1997)	This research plan describes ORD's research to support EPA's drinking water regulations concerning disinfectants, disinfection by-products, and microbial pathogens. The research plan identifies key scientific and technical information gaps and provides guidance to both intramural and extramural research programs regarding priorities and sequencing of research.
Research Plan for Arsenic in Drinking Water (U.S. EPA, 1998a)	This research plan provides guidance to improve the scientific understanding of health risks associated with arsenic in drinking water and to support improved control technologies for water treatment.
Strategic Research Plan for Endocrine Disruptors (U.S. EPA, 1998b)	This research plan addresses research needs of biological effects for human health and wildlife and exposure assessment of endocrine disruptors. Integration of effects and exposure research is emphasized to provide a complete analysis of risk.
Airborne Particulate Matter Research Strategy (U.S. EPA, 1999)	This research strategy describes health, exposure, risk assessment, and management research on particulate matter to support EPA's review and implementation of the National Ambient Air Quality Standards.
Strategy for Research on Environmental Risks to Children (U.S. EPA, 2000a)	This research strategy describes future directions and priorities of ORD's program to reduce uncertainties in EPA risk assessments for children, leading to effective measures to prevent and/or reduce risk.

Mercury Research Strategy (U.S. EPA, 2000b)	This strategy presents the scientific questions and research goals and priorities for EPA's research program on mercury.
Asthma Research Strategy (U.S. EPA, 2000c)	This strategy describes the research directions and priorities to improve the scientific understanding of environmental factors underlying increased risk for asthma and to develop more effective risk management control technologies to reduce and prevent asthma cases.
Air Toxics Research Strategy (U.S. EPA, 2000d)	This strategy presents research approaches and objectives to improve the scientific and technical knowledge base for the assessment and management of health risks of hazardous air pollutants.
Drinking Water Contaminants Candidate List (CCL) Research Plan (U.S. EPA, 2000e)	This plan describes the research approach and process to provide improved scientific and technical bases for the assessment and management of drinking water contaminants that are on the CCL.

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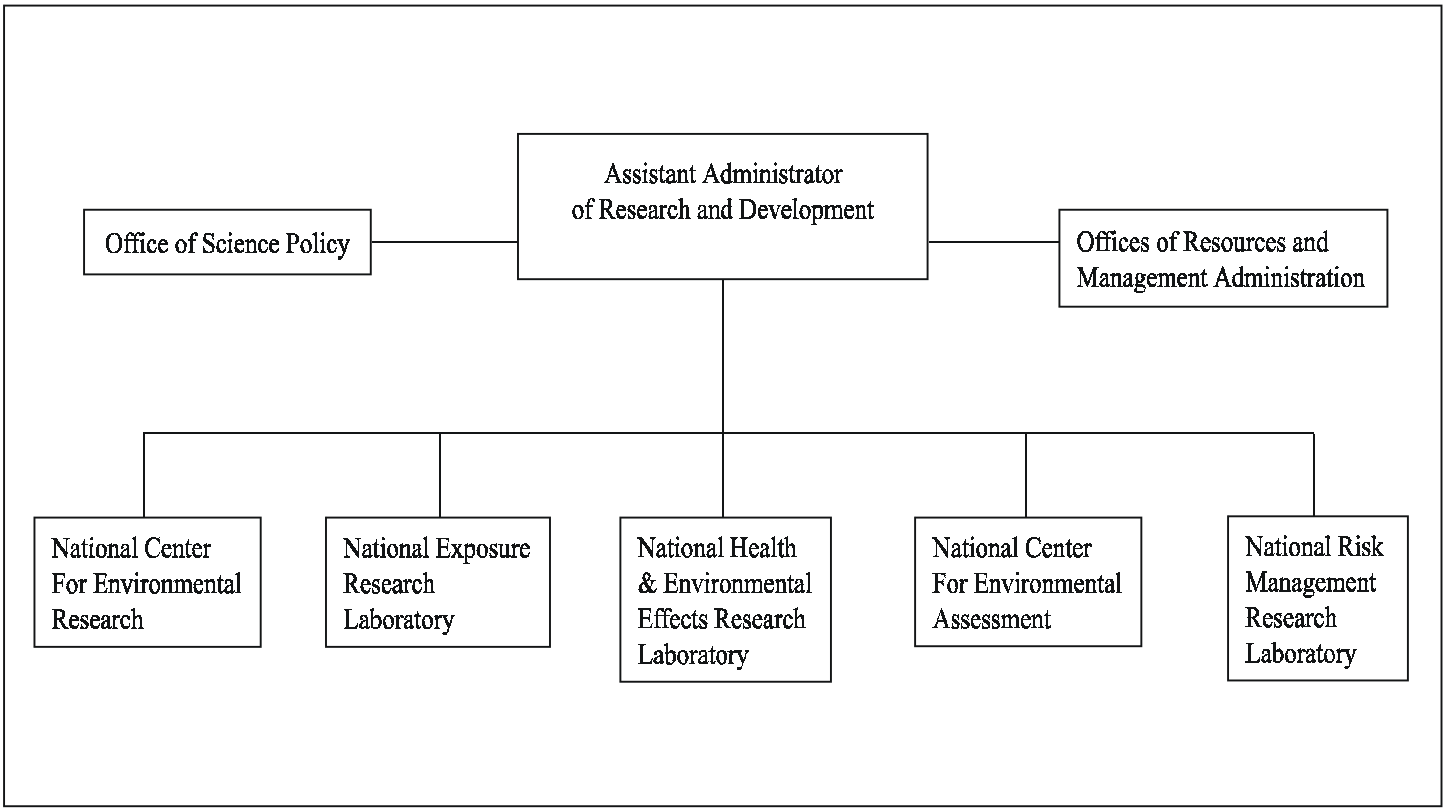
APPENDIX B

EPA's Office of Research and Development—Organizational Chart



APPENDIX C

Examples of Mechanistic Data Used in Risk Assessment

Pollutant	Supporting Research
Aflatoxin B1	Mechanistic studies showed that this compound forms DNA adducts and protein adducts, causing specific mutations in the p53 tumor suppressor gene. Because of this mechanistic information, formation of DNA adducts is now being used to assess cancer risk in human populations.
Dioxin	The understanding that essentially all the effects of dioxin are mediated via binding to the arylhydrocarbon (Ah) receptor provides the underpinning for the species extrapolation in the risk assessment of dioxin. The Ah receptor is highly conserved, present, and functional in nearly all vertebrates. The current consensus that dioxin is a known human carcinogen is based on clear animal data, limited human data, and the presence of a common mechanism of action.
Dioxin	The importance of PBPK models for risk assessment is illustrated by the identification of an inducible hepatic binding protein by dioxin, which results in dose-dependent sequestration of dioxin in multiple mammalian species, including humans. This information has allowed for a better understanding of the dose-dependent differences in the disposition of dioxin, which has led to the conclusion that body burden is the best dose metric for risk assessment of dioxin and related compounds. This approach allows for a direct comparison of animal and human data, which reduces the animal-to-human uncertainty in risk assessment.
d-Limonene	A number of chemicals (e.g., d-limonene) and chemical mixtures (e.g., unleaded gasoline) induce kidney tumors in male rats in cancer bioassays. Mechanistic studies have shown that kidney tumors in male rats are associated with an increase in the level of a specific protein, a2μ-globulin. Because this protein is not present in human male kidneys, risk assessors could predict that the cancer risk in humans for chemicals acting via an alpha 2μ-globulin-mediated process will be low.
Atrazine	Research from ORD showed that the effects of atrazine on mammary gland and prostate development are associated with alterations in the hormone prolactin. This mechanistic information is currently being used to reevaluate the risk assessment for atrazine.

APPENDIX D

Agencies Having Research Programs Complementary to ORD

The National Institute of Environmental Health Sciences (NIEHS achieves its mission through multidisciplinary biomedical research programs, prevention and intervention efforts, and communication strategies that encompass training, education, technology transfer, and community outreach. For example, the NIEHS program includes a trans-NIH effort to study effects of chemicals, including pesticides and other toxics, in children. EPA has collaborated with NIEHS in establishing Centers for Children's Environmental Health and Disease Prevention to define the environmental influences on asthma and other respiratory diseases, childhood learning, and growth and development. NIEHS and the National Institute of Allergy and Infectious Diseases (NIAID) are conducting the Inner-City Asthma Study, which is a prevention trial to develop an intervention strategy to reduce asthma morbidity in inner-city children and adolescents. The National Allergen Study, being conducted by NIEHS in collaboration with the Department of Housing and Urban Development (HUD), examines the relationship between allergens and lead and how allergen exposures differ as a function of geographic region, socioeconomic status, housing type, and ethnicity. NIEHS and the National Toxicology Program (NTP) develop new technologies for high-throughput toxicity testing, and these agencies are responsible for one-third of all toxicity testing performed worldwide. Long-term collaborative efforts with NTP, particularly in the areas of carcinogenesis, reproductive/developmental toxicity, and neurotoxicity, are well established. NIEHS has established the National Center for Toxicogenomics (NCT) to coordinate an international research effort to develop the field of toxicogenomics. The NCT will provide a unified strategy, a public database, and develop the informatics infrastructure to promote the development of the field of toxicogenomics. NIEHS will pay special attention to toxicogenomics as applied to the prevention of environmentally-related diseases.

The **National Cancer Institute (NCI)** conducts population-based research on Environmental and genetic causes of cancer and on the role of biological, chemical, and physical agents in the initiation, promotion, or inhibition of cancer and the biological and health effects of exposure to radiation.

The **Centers for Disease Control and Prevention (CDC),** through the National Center for Environmental Health (NCEH), studies health problems associated with human exposure to lead, radiation, air pollution, and other toxicants, as well as to hazards resulting from technologic or natural disasters. These are mainly surveillance and epidemiology studies. NCEH is particularly interested in studies that benefit children, the elderly, and persons with disabilities. The National Center for Health Statistics (NCHS) of CDC is conducting the National Health and Nutrition Examination Survey (NHANES). NHANES is a national population-based survey and includes data on potentially sensitive subpopulations such as children and the elderly. EPA is participating in this survey with NCHS to collect information on children's exposure to pesticides and other environmental contaminants. CDC's *National Report on Human Exposure to Environmental Chemicals* is a new publication that provides an ongoing assessment of the exposure of the U.S. population to environmental chemicals using biomonitoring data collected through NHANES. The first Report provides information about levels of 27 chemicals.

The **National Institute of Child Health and Human Development (NICHD)** supports laboratory, clinical, and epidemiological research on the reproductive, neurobiological, developmental, and behavioral processes that determine and maintain the health of children and adults. ORD is collaborating with NICHD, CDC, and other Federal agencies in the design and implementation of a National Children's Study of 100,000 children, who will be enrolled during the mother's pregnancy and followed throughout childhood and adolescence. This study was mandated in the Children's Health Act of 2000 to study environmental influences on children's health and development.

The **National Center for Toxicological Research (NCTR)** supports fundamental research on the effects of chemicals regulated by the Food and Drug Administration. Although some of the models used by NCTR may be similar to those used by EPA, the chemicals and regulatory context vary significantly. Historically, NCTR has been a leader in developing models and principles for risk assessment, which has led to collaborations between EPA and NCTR scientists.

APPENDIX E

Examples of Health and Environmental Databases to Evaluate Public Health Outcomes From Risk Management Actions

Environmental Databases		
Source	**Database Name**	**Contents**
EPA/ORD	NHEXAS	Exposure data for Arizona, EPA Region V, and Baltimore
EPA	SDWIS/FED	Regulated pollutant concentration in drinking water
EPA	STORET	Surface water quality/biological monitoring
EPA/OAQPS	AIRS	Air pollutant concentrations at 4,000 sites; 9,000 point sources
EPA	ETS	Emissions from electric utilities
EPA	Center for Environmental Information and Statistics	Central source of environmental data/trends
EPA/OPPTS	TRI	Toxic compounds release inventory
EPA	CERCIS	Hazardous waste sites, assessment, and status
EPA	BASINS	Watershed pollutants (point and area source) and locations

Health Effects Databases		
EPA/ORD	IRIS	Hazard characterization and risk numbers for cancer and noncancer endpoints
NCI	SEER	Cancer incidence/prevalence by type and location
CDC	Various	Incidence of contagious diseases
Veterans Administration	VA databases	Major disease incidence and prevalence by location
National Center for Health Statistics	NHANES	Prevalence and incidence data in populations
State Health Departments	Various	Disease incidence by location and time
Insurance Companies	Various	Disease and death incidence by location, time, and population
Health and Environmental Databases		
EPA, Region 3	Green Communities Initiative	Environmental health, economic, and societal indicators of impact of environmental regulation
ATSDR	HazDat	Relationship between exposure to hazard and effect